

Occupational upper airway disease

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Purpose of review

This article reviews recent findings concerning occupational upper airway diseases, which, although very frequent, are usually not considered serious. However, the concept of the 'united airway', evoked during recent years, should change our attitude regarding these diseases. Moreover, new agents in the occupational environment must be characterized. Furthermore, exposure to carcinogens has changed over the years, and in most cases risk should be reassessed.

Recent findings

Recent findings concerning work-related upper airway diseases caused by allergens and irritants, and their relationship to lower airway diseases, are reviewed. Findings of studies aimed at characterizing occupational allergens of plant and animal origin are presented. Recognition of work-related upper airway diseases both in clinic and in epidemiological studies is discussed. Current evidence on occupational cancer of the upper airways, its risk factors and changes in them over the years resulting from preventative measures are also described.

Summary

There is significant evidence that occupational allergic diseases of the upper airways can pose important health problems because they represent an early stage of allergy throughout the respiratory system. However, how to detect those rhinitic patients who will develop asthma remains unresolved. New occupational health problems due to irritants were recently reported, and both follow-up studies and evaluations of their implications for the lower airways are warranted. Although preventative measures have been effective to some extent, risk for occupational cancer of the upper airways persists and more targeted epidemiological studies in this area are needed.

Keywords

diagnostics, irritants, occupational allergy, occupational cancer, upper airway

Abbreviations

CI	confidence interval
eNO	exhaled nitric oxide
NLF	nasal lavage fluid
OR	odds ratio
RADS	reactive airways dysfunction syndrome
RR	relative risk
RUDS	reactive upper airways dysfunction syndrome
SPT	skin prick test

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Introduction

The upper airways are a portal of entry for workplace-related hazardous materials into the respiratory system. Allergens, irritants and carcinogens can all cause occupational diseases of the upper airways. Such diseases, especially those induced by allergens and irritants, are usually not considered serious. However, the concept of the 'united airway', evoked in recent years, may change our attitude toward them. The most important link between rhinitis and asthma is the presence of inflammation of the nasal and bronchial mucosae [1]. Local allergen challenge can induce allergic inflammation in the entire airway system, irrespective of the site of allergen application [2,3]. Up to 40% of patients with allergic rhinitis also have asthma, and as many as 80% of patients with asthma suffer from nasal symptoms [4]. However, the contention that allergic rhinitis is a risk factor for development of asthma is not entirely correct, because rhinitis may represent an early stage in united airway disease, and subsequent onset of asthma may be a further component in its evolution [5]. Regarding upper and lower airways as one functional entity has diagnostic and therapeutic implications. In the light of this approach, when qualifying into vocational training and work, individuals with allergic rhinitis should be treated in the same way as those with asthma.

Allergic diseases frequently attract the interests of researchers, but the effects on health of exposure to irritants and carcinogens are less investigated. Data on the nose-lung link in persons exposed to such agents are lacking. Moreover, new agents are introduced into the occupational environment before their effects have been fully characterized. Furthermore, exposure to carcinogens has changed over the years, and in most cases risk should be reassessed. Development of diagnostic tools that can be used in epidemiological studies is also

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needed. This review summarizes recently reported findings concerning these issues.

Is occupational allergy of the upper airway a serious problem?

Although researchers pay far less attention to allergy of the upper airways than to allergy of the lower airways, the prevalence of allergic rhinitis – the most common upper airways chronic disease – continues to increase [6], and it is currently the most frequent and troublesome allergic disorder in westernized countries [7]. Moreover, quality of life was found to be worse among patients with rhinitis than among those with asthma [8,9].

Problems with epidemiological data

Even though data on the prevalence of occupational rhinitis are limited, it has been reported to be high, ranging from 5% to 65% [10]. At least in part, discrepancies between data on the prevalence of occupational allergy can be accounted for by differences in diagnostic criteria and techniques. For instance, there is no general agreement on the definition of rhinitis used in epidemiological studies. The definition adopted by the European Community does not include rhinitis caused by low-molecular-weight allergens [11].

In a recent Finnish study conducted in 254 individuals exposed to laboratory animals [12^{••}], specific sensitization was a frequent cause of occupational rhinitis. Allergic rhinitis was identified in 32% of individuals reporting such symptoms, and positive skin prick tests (SPTs) to laboratory animals were found in 51% of the group. Curiously, occupational disease was diagnosed more frequently among researchers than among other animal workers. On the other hand, Gautrin *et al.* [13] reported that only three out of 30 apprentices with work-related symptoms of rhinoconjunctivitis had been sensitized to flour.

Follow-up studies conducted in individuals without prior exposure provide the most valuable information on the incidence of and risk factors for occupational allergy. However, they are difficult to perform because of attrition of participant numbers over time. Moreover, in most studies diagnosis of occupational rhinitis is based on questionnaire data and SPT results. A recent study conducted in a group of apprentice bakers employed specific challenge tests for clinical verification of the reported symptoms [14[•]]. The incidence of occupational rhinitis was found to be high (8.4% after 1 year and 12.5% after 2 years of vocational training). Interestingly, the latent period until development of rhinitis was almost the same as that until the first chest symptoms (13.5 ± 6.6 versus 13.6 ± 4.3 months, respectively). Although allergic rhinitis is usually thought to precede bronchial asthma [15], in the group reported both occurred almost

simultaneously. The question arises, then, of whether allergic march also occurs in occupational allergy. A limitation of that study is that the data were based on participant recollection, so it is possible that the patients may not have noticed rhinitis symptoms early enough as they are less worrying than the chest symptoms.

Identification of individuals who are at risk for developing airway disease

Identifying workers who may develop allergic rhinitis as a result of exposure to agents in the workplace, and those rhinitic patients who will develop asthma, remains one of the biggest problems in occupational allergology. In a study mentioned above [14[•]], skin hyperreactivity to common allergens was found to be a risk factor for occupational rhinitis, but its positive predictive value was only 37%, whereas the negative predictive value was 93.1%.

The only reported prospective study on risk for asthma among individuals with already diagnosed occupational rhinitis included 3637 nonasthmatic patients [16]. Of these patients 11.6% were diagnosed with asthma during the follow-up period, as compared with 3.1% of the 31 457 persons in the reference population (individuals with occupational disease other than occupational rhinitis, asthma, allergic alveolitis and allergic contact dermatitis). The crude relative risk (RR) for asthma was 4.8 [95% confidence interval (CI) 4.3–5.4]. The adjusted RR for asthma among rhinitic patients was the highest for farmers and wood workers [RR 6.8 (95% CI 5.5–8.2) and RR 7.0 (95% CI 3.5–14), respectively], although the interaction was significant for all occupations.

The findings of these studies, as well as those of earlier prospective studies on risk factors for occupational allergy [17–19], suggest that there is a need to identify and screen high-risk workers, and – when necessary – tailor intervention programmes for them. However, we still do not know which of them will develop asthma.

Clinical verification of occupational allergy

Diagnosing occupational allergy often means dealing with patients who are claiming compensation, and therefore it requires objective methods. Coexistence of nasal and bronchial allergic inflammation makes diagnosis easier. A recent comparison of changes in nasal lavage fluid (NLF) in bakers with occupational respiratory allergy revealed a slightly (but not significantly) more pronounced response to allergen challenge in individuals suffering from asthma and rhinitis than in patients with rhinitis alone [20]. This may suggest that the inflammatory process was more intensive in longer lasting disease including the whole respiratory system. Also, Boulay and Boulet [21] reported that nonasthmatic patients with

allergic rhinitis exhibited a reduction in airway inflammation following repeated inhalation of very low doses of allergen, even when the exposure to allergen was continued. Nevertheless, evaluation of NLF, although very sensitive and specific, cannot be used to distinguish between patients with upper and lower airway allergy. It should also be noted that evaluation of nonspecific bronchial hyperresponsiveness may not always discriminate between asthmatic and rhinitis patients, because patients with allergic rhinitis often exhibit nonspecific bronchial hyperreactivity [22].

Examining large occupational groups requires reliable diagnostic tools that could be added to questionnaires and spirometry. Recently, measuring exhaled nitric oxide (eNO) was suggested to be a useful marker of airway inflammation in epidemiological studies. The study, conducted among 246 workers from bleaching departments of pulp mills and paper mills, found that only atopic individuals who had recently been exposed to the relevant allergen had elevated levels of eNO [23^{••}]. Atopic individuals who are not exposed to a relevant allergen or have never experienced symptoms of asthma and rhinitis exhibit normal eNO levels. Thus, eNO relates only to airway inflammation in atopic individuals, which means that it can be used in research into occupational allergy resulting from exposure of atopic individuals to high-molecular-weight allergens.

Occupational allergens: new problems

Plant allergens are a diverse and incompletely characterized group of potent allergens. Interestingly, some of them pose a higher risk to the upper than to the lower airway. Chloros *et al.* [24[•]] evaluated 1020 seasonal and nonseasonal tobacco workers, and found an association between diseases of the upper airways (but not lower ones) and tobacco dust. The prevalence of rhinitis was reported to be significantly greater than in the control group (27.3% versus 17.9%). However, only six workers were sensitized to dried tobacco leaf dust. No cases of bronchial asthma were identified. Similarly, Chatzi *et al.* [25[•]] demonstrated a high prevalence of allergic rhinitis in grape farmers (45.8%) and a twofold greater risk for allergic rhinitis in comparison with a control group, whereas the prevalence of asthma was 6.7% and did not differ significantly from that in the control individuals. Approximately half of the exposed group exhibited positive SPT or specific-serum IgE to common and occupational allergens.

Over recent years interest in asparagus as an allergen has grown. In 2000 more than 4 million tonnes of asparagus were grown in the world. It is a causative agent in such occupational diseases as contact dermatitis, asthma and rhinitis. An evaluation of immunoblotting pattern and SPT responses to asparagus allergens relative to clinical

symptoms in 27 patients [26^{••}] revealed that two lipid transfer proteins, namely Aspa o 1.01 and Aspa o 1.02, probably play a role in the most severe symptoms (anaphylaxis and occupational asthma), whereas other asparagus proteins were implicated in patients with mild symptoms (rhinitis, contact urticaria and oral allergy syndrome). The authors also suggested that the limited number of case reports published may be the result of under-diagnosis rather than low frequency of asparagus allergy.

Flowers are another source of potent allergens. Akpinar-Elci *et al.* [27^{••}] evaluated work-related respiratory symptoms among 128 florists working in floral shops. Rhinitis was reported by 13.3% of individuals. Hypersensitivity to a mixture of flower allergens was identified in 9.4%. An excess risk for work-related asthma-like symptoms was found among workers with allergic conjunctivitis and rhinitis [odds ratio (OR) 13.3, 95% CI 3.1–56.4].

Throughout the past decade allergic reactions to a wide range of plants in individuals sensitized to natural rubber latex have become a focus of attention. Recently, cross-reactivity between latex proteins and obeche wood has also been demonstrated using Immuno-CAP inhibition [28^{••}]. Obeche extract partially inhibited the Hev b 6.02 response, which suggests that hevein-like domains in obeche proteins are responsible for the cross-reactivity between latex and obeche wood. This finding implies that there is a need for increased awareness of potential natural rubber latex allergy among patients sensitized to plant allergens.

Allergy to insects has been recognized as an important occupational medicine problem, but the diversity of possible allergens and the low numbers of individuals exposed to each of them have resulted in very limited data. Thus, new case reports are of great value. A case of rhinoconjunctivitis induced by deer ked (*Lipoptena cervi*; which belongs to the louse fly family) in a researcher working in a geological institute has been described [29[•]]. The symptoms occurred even when the patient managed to avoid insect bites. The recognition of allergy was confirmed by the results of specific nasal and conjunctival provocation tests, immunoblotting and immunoblot inhibition studies. In addition, locust species have been proved to be potent allergens [30]. Seven out of 10 exposed laboratory workers were reported to have positive SPTs to *Locusta migratoria*, and in five specific IgE was found. Six of them experienced symptoms ranging from urticaria and rhinoconjunctivitis to asthma. The immunoblotting of all sera revealed strong IgE binding to a 70 kDa protein contained in locust wings.

Further interesting recent findings pertain to beekeepers. Rudeschko *et al.* [31[•]] suggested that inhalation of a fine

powder released from brittle mummified larvae and dead bees, which is present in the air during the handling of honeycombs in hives, may induce rhinoconjunctivitis. A 13 kDa protein that is present both in bee bodies and in larvae has been isolated as an inducer of these reactions. It was also stressed that, despite class 2 specific IgE to bee venom, the patient was free from clinically relevant symptoms after bee stings. However, there is no evidence regarding whether the case described is a singular phenomenon or whether it is more common among those exposed to honeybees.

During the review period cases of rhinitis due to Wonji made from the root of *Polygala tenuifolia*, *Tilia cordata* (linden) and seminal fluid from bull terriers have also been reported [32–34].

Irritants: new hazards

The upper airways were among the target organs of airborne pollutants present at the World Trade Center site. Irritant effects on the airway in rescue workers have attracted much attention.

Reactive upper airways dysfunction syndrome (RUDS), an upper airways analogue of reactive airways dysfunction syndrome (RADs), is defined as chronic rhinitis triggered by high-level exposure to inhaled irritants [35]. Although the definition of RUDS is very similar to that of RADs, objective criteria for RUDS recognition – in contrast to RADs – are not well defined [36]. High rates of upper airway symptoms have been described in various occupational groups involved in rescue, recovery and clean up at the World Trade Center site [37•]. The frequency of ear, nose and throat symptoms ranged from 78% at 4 weeks after the World Trade Center collapse to about 50% at least 8 months after exposure ended [36,37•]. Most of the reported symptoms were probably due to RUDS. Further investigations into the natural history of RUDS would be of great interest.

Changes in the painting industry (e.g. use of powder painting instead of solvent-based spray painting) might have resulted in changes in the prevalence of respiratory symptoms and immunologic responses among powder painters. The organic acid anhydrides, which are used as curing agents in the production of epoxy resins, are both allergens and irritants to the airways [38]. A study conducted by Blomqvist *et al.* [39] included 93 exposed powder painters, 26 formerly exposed persons and 86 unexposed workers. Nasal symptoms were frequently reported by highly and formerly exposed individuals (e.g. sneezing in 40% and 46%, and nasal blockage in 35% and 54%, respectively). The frequency of airway symptoms reported by the low-exposure group was similar to that in unexposed individuals. Specific IgE against phthalic acid and trimellitic anhydride were not

found. Exposure to organic acid anhydrides was evaluated to be low during regular working conditions in the powder paint shops. The work-related symptoms were probably caused by irritative properties of high levels of powder paint dust, although an effect of curing agents cannot be excluded.

A study in which a questionnaire was completed by 4100 Finnish painters and a population of 14 900 carpenters (control group) [40] revealed higher prevalence rates for rhinitis and laryngeal symptoms in painters than in control individuals (45.4% versus 33.3% and 15.5% versus 10.5%, respectively). However, occupation was not associated with allergic rhinitis.

Ozone is now often used as a replacement for chlorine and chlorine dioxide as bleaching agents or disinfectants (e.g. at swimming pools). Whereas many studies have shown a link between exposure to ambient levels of ozone and asthma [41,42], data on upper airways were lacking. Hoffman *et al.* [43•] reported an increased risk for noninfectious rhinitis among individuals exposed to high levels of ozone, which reveal a need to avoid peak concentrations. However, investigations into the effects of exposure to lower concentrations of ozone would be greatly appreciated.

Biological agents and their influence on human health are currently in focus. Upper respiratory inflammation may be one of many effects on health of exposure in the household waste recycling industry. Hørdal *et al.* [44] found that an increase in neutrophils correlated significantly with myeloperoxidase, eosinophil cationic protein and interleukin-8 levels in NLF, as well as with swelling of the nasal mucosa. Although the population examined was relatively small, the study provides evidence that symptoms caused by bio-aerosol containing bacteria, endotoxin, fungal spores and $\beta(1\rightarrow3)$ -glucans induces nonallergic inflammation of the upper airways. The implications of this finding, especially regarding any influence on the lower airways, should be evaluated in further investigations.

Occupational cancer: is there still risk?

The rarity of occupational cancer, greater mobility among populations and more frequent job changes make it difficult to conduct epidemiological studies to establish whether there are any associations between occupation and cancer. Furthermore, research is needed even for well recognized carcinogens because risk for cancer might have diminished with improved industrial safety legislation.

Recently, additional data concerning the risk for cancer of the larynx among unskilled workers in the printing industry (standardized incidence ratio 2.03, 95% CI

1.20–3.21) [45], meat industry workers (OR 2.0, 95% CI 1.2–3.4) [46], and individuals exposed to solvents (OR 2.8, 95% CI 1.5–5.1) and formaldehyde (OR 2.3, 95% CI 1.1–4.6) [47] have been reported. However, the term ‘solvent’ comprises a number of different compounds, and it has not been identified which one of them is involved in larynx carcinogenesis. Earlier studies suggested an association with paint [48,49], but further investigations into this correlation are required. Also, an association between occupational exposure to asbestos and cancer of the larynx (OR 1.8, 95% CI 1.2–2.5) was found [47].

Wood dust has been classified by the International Agency for Research on Cancer as a human sinonasal carcinogen, based on a substantial number of studies [50]. However, a recent study conducted by Berrino *et al.* [47] revealed decreased risk among individuals younger than 55 years, whereas those investigators estimated that there was nearly a twofold excess risk among men born before 1925. It is possible that changes in wood processing and duration of occupational exposure were sufficient preventative measures. On the other hand, because sinonasal tumours are very rare, Bimbi *et al.* [51] used a different approach to recognition of this relationship. Analysis of 499 patients with sinonasal tumours revealed that ethmoid adenocarcinoma significantly correlated with exposure to wood or leather. The authors postulate that ethmoid adenocarcinoma should be suspected in all patients with a history of nasal obstruction and/or nose bleeding who are exposed to wood and leather dust.

Conclusion

Studies reported over recent years have improved our knowledge of the occupational diseases of the upper airways and demonstrate the following main points. First, there is increasing evidence that occupational allergic diseases of the upper airways should not be considered less serious than other disorders because they represent an early stage in allergy of the entire respiratory system. There is an urgent need to determine the risk for asthma in a worker with rhinitis who is continuing to be exposed to occupational allergens. An important issue is whether it is possible to detect which rhinitic patients will develop asthma. Second, data regarding whether the term ‘united airway disease’ can also be applied to irritant-induced diseases are still needed. During recent years new occupational health problems due to irritants emerged, and so follow up as well as studies focusing on their implications for the lower airways are needed. Finally, although preventative measures have been effective to some extent, the risk for occupational cancer of the upper airways persists. Therefore, more targeted epidemiological studies in this area, complemented by experimental studies into the specific pathogenetic mechanisms by which

workplace hazards exert their harmful effects, should be undertaken.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 67–68).

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