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REVIEW ARTICLE

Occupational upper airway disease: how work affects the nose

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Abstract

Chronic inflammation of the upper airways is common and can arbitrarily be divided into rhinitis and rhinosinusitis. Infection and allergy represent two well-characterized and most frequently diagnosed etiologies of upper airway inflammation. Persistent upper airway inflammation caused by agents inhaled in the work environment represents a diagnostic challenge in clinical practice, and its pathophysiology has been little studied. Occupational rhinitis is a recognized medical condition with diagnostic and therapeutic guidelines. In contrast, only limited evidence is available about the relationship between work exposures and rhinosinusitis. This review aims at providing a comprehensive overview of the available literature on occupational upper airway disease with a focus on pathophysiological mechanisms and with an emphasis on the current unmet needs in work-related upper airway disease.

Rhinitis affects 30% of the Western population and causes invalidating symptoms such as nasal obstruction, rhinorrhea, sneezing, itchy nose (1). When the inflammation extends to the paranasal sinuses, it causes typical additional symptoms of rhinosinusitis, that is, headache and smell dysfunction (2).

At the entry of the airway, the nasal mucosa is continuously exposed to a variety of airborne substances present in the environment. These include the common aeroallergens that cause allergic rhinitis in atopic individuals, but also air pollutants, as well as numerous agents encountered at the work floor. The airways are the primary target for a variety of work-related dusts, gases, fumes, and vapors. Depending on the amount inhaled and their physical–chemical properties, these agents can cause irritation, corrosive changes, and/or sensitization of the respiratory mucosa (3). Occupational rhinitis is defined as an inflammation of the nasal mucosa due to causes attributable to a particular work environment (4) and has to be distinguished from 'work-exacerbated rhinitis', which refers to a pre-existing rhinitis that is exacerbated by workplace exposures (5). The term 'occupational rhinosinusitis' has been proposed only recently (6), and very limited data exist on the impact of occupational agents on sinus disease. Yet it makes sense to assume that the sinus cavities can also be affected by exposure to occupational agents because the mucosa of the nose and paranasal sinuses are so closely linked anatomically and they share similar inflammatory profiles.

When patients with occupational rhinitis remain exposed to the causal agent, they may progress to asthma (7), suggesting that timely recognition of occupational rhinitis plays a role in the prevention of occupational asthma. However, occupational rhin(osinus)itis is still a poorly researched area in the field of chronic upper airway disease. Therefore, this review aims at providing a comprehensive overview of what is currently known about occupational inflammatory upper airway disease with a focus on pathophysiological mechanisms and highlighting the gaps that remain in this area.

Estimated prevalence of occupational upper airway disease

In contrast to occupational asthma, occupational rhinitis has received attention only in recent years.

The close link between the upper and lower airways has been known for decades, and inflammation in one part of the airway influences the homeostasis of the other, a phenomenon that is referred to as 'global airway disease' (8). It is known that up to 90% of individuals with asthma suffer from rhinitis and one-third of patients with allergic rhinitis suffer from asthma (9). A large longitudinal study based on the European Community Respiratory Health Survey showed a relative risk of developing asthma of 2.71 for non-allergic rhinitis patients and of 3.53 for patients with allergic rhinitis, making rhinitis a powerful predictor of adult-onset asthma (10). Chronic rhinosinusitis (CRS) has also been associated with adult-onset asthma (11). Available epidemiological data suggest that this is no different in the occupational airway disease field; upper airway symptoms are present in up to 92% of subjects with occupational asthma (12), and they seem to precede lower airway symptoms in 58% of asthma induced by high molecular weight agents and 25% of low molecular weight agents (13). However, the lack of good population-based studies applying a correct definition of rhinitis and rhinosinusitis has precluded knowing the prevalence of occupational upper airway disease without (reported) asthma. So, we can only speculate about the attributable risk of occupational exposure in chronic upper airway disease. Based on known epidemiological data on nonoccupational asthma and rhinitis, occupational upper airway disease is estimated to occur two to three times more often than occupational asthma (1, 5), which suggests that occupational rhin(osinus)itis must be considerably underdiagnosed. The reasons for this include the current lack of validated diagnostic tools and the reluctance of patients to complain about their occupational environment for fear of losing their job.

Some surveys investigated the prevalence of occupational rhinitis among different working populations. These studies are usually too small to directly study the occurrence of occupational rhinitis in the general population, but they give an idea about its high prevalence in some specific work sectors which is summarized in Table 1.

Only very few studies have focused on the occurrence of sinus symptoms in relation to work. Zuskin et al. performed several surveys in specific work sectors such as paper recyclists, textile and pharmaceutical workers and found a clear relationship between sinusitis symptoms and work-related exposures (14, 15). However, the questionnaire did not fully cover the current definition of rhinosinusitis (2). Follow-up studies of workers present at the WTC disaster site revealed that sinusitis symptoms were reported in 50% of iron workers (16) and 48% of firefighters (17). Our recent retrospective study of 467 patients with rhinosinusitis who had undergone functional endoscopic sinus surgery (FESS) (6) revealed not only that relevant occupational exposures were twice more frequent among these patients with rhinosinusitis than their controls (25% *vs* 12%, respectively), but also that the proportions of subjects with relevant occupational exposures rose significantly ($P < 0.001$) with the number of FESS. Although this retrospective study does not prove that occupational agents caused rhinosinusitis, it provides strong evidence that occupational exposures are involved in the more severe forms of rhinosinusitis.

Table 1 Prevalence and etiological agents in occupational rhinitis [adapted from references (5) and (12)]

Occupation	Prevalence (%)
Laboratory workers	9–42
Swine confinement workers	8–23
Laboratory and farm workers	2–60
Grain elevators	28–64
Bakers	18–29
Hospital workers, textile factory	9–20
Tobacco, tea, coffee, cocoa, dried fruit, grapes and saffron workers, greenhouse workers	5–54
Pharmaceutical and detergent industry	3–87
Trout, prawn, shrimp, crab, clamps workers, aquarists, fish-food factory workers	5–24
Painters, urethane mold workers	36–68
Epoxy resin production, chemical workers, electrical condenser workers	10–48
Carpentry and furniture making	10–36
Platinum refinery	43
Healthcare and pharmaceutical workers	9–41
Hairdressers	27
Reactive dye, synthetic fiber, pulp and paper, shoe manufacturing, automotive manufacturing	3–61
Cleaners	35

Occupational factors related to upper airway inflammation

Occupational agents capable of causing symptomatic airway inflammation are traditionally classified as either high molecular weight (HMW) (>5 kDa) or low molecular weight (LMW) agents (<5 kDa) (18). HMW agents are biological substances derived from plants or animals, such as flour, latex, mites, laboratory animals, and other sources. These agents can cause airway inflammation via the well-known IgE-mediated immune response leading to a T-helper (Th) 2-driven inflammation, as is the case for nonoccupational aeroallergens, such as pollens and house dust mite (Fig. 1). The mechanisms by which LMW substances can induce airway inflammation are far less known. LMW agents can be subdivided into two groups, according to their sensitizing capacity.

With the LMW agents that are capable of airway immune sensitization, a latency period of weeks to years is observed between initial exposure and symptoms. They are synthetic chemicals, with the most common ones being di-isocyanates (polyurethane foams or coatings), persulphate salts (hair bleachings), acid anhydrides (epoxy resins), some aldehydes (glutaraldehyde), and several drugs. Various metallic agents (platinum salts, chromium, nickel) and woods (plicatic acid in Western red cedar) can also act as airway sensitizers.

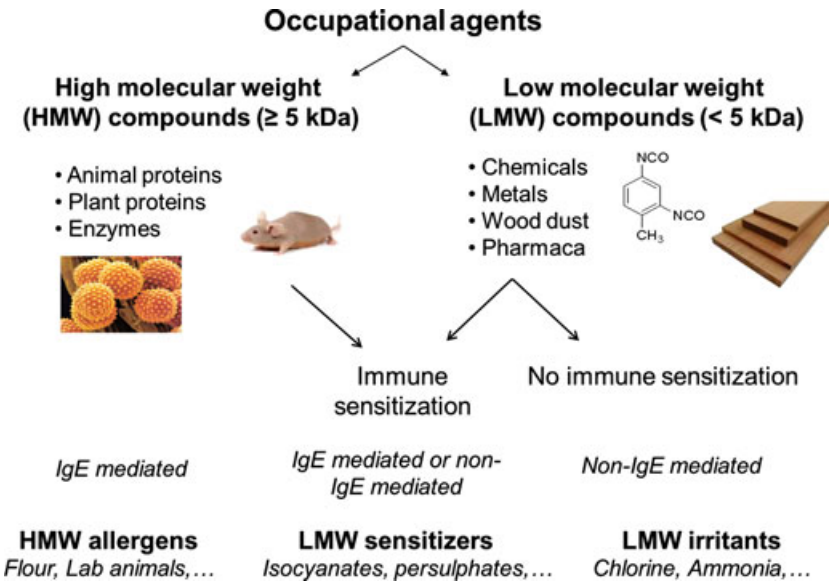

Figure 1 Scheme listing the three classification groups of occupational agents capable of inducing occupational airway disease according to their pathophysiological mechanisms.

Many LMW agents are capable of inducing mucosal inflammation without evidence of a latency phase or immunological sensitization, and these agents are called 'irritants' (Fig. 1) (19). The definition of a sensory irritant is based on the fact that the chemical, upon inhalation, will stimulate trigeminal nerve endings and inhibit respiration, which is shown by the Alarie test (20). The most common and best known irritants are chlorine and chlorination products, ozone, acids, and ammonia, but the list is extensive. Acute accidental exposure to irritants is known to lead to inhalation injury. Water-soluble gases as well as larger particles (>10 μm) affect mainly the upper airways, while poorly water-soluble gases and smaller particles reach the lower airways. A single acute inhalation injury may lead to asthma without latency which has been labeled 'reactive airways dysfunction syndrome' (RADS) (21). By analogy, the concept of 'reactive upper airway dysfunction syndrome' (RUDS) was created to describe a condition of persistent upper airway symptoms, such as nasal blockage, runny nose, or sneezing, initiated following acute injury to the upper airways (22). Unlike RADS, which is now an established clinical entity, RUDS is still a rather obscure condition with unknown incidence and prevalence.

Recently, it has been suggested that not only acute inhalation of high concentrations of irritants can have a detrimental effect on the airways, but also long-term exposure to lower irritant concentrations might induce a more chronic dysfunction of the airway mucosa. For example, cleaners (23), swimming pool workers (24), and competitive swimmers (25) who are chronically exposed to chlorination products show more upper airway symptoms compared to nonexposed persons. Similar findings have been shown in beverage-processing plant workers who are chronically exposed to low amounts of hydrogen peroxide (26).

Pathophysiological mechanisms involved in occupational airway disease

Effects of inhaled occupational allergens on the adaptive immune system

The airway inflammation caused by HMW agents follows the well-known paradigm of allergic sensitization to common aeroallergens, with Th2-mediated mechanisms (27). The inhaled allergens are taken up by dendritic cells in the airways and presented to naïve $CD4^+$ lymphocytes in the lymph nodes. The local cytokine environment together with the activation of the $CD4^+$ cells causes a shift toward the Th2 subtype with the production of Th2 cytokines such as IL-4, IL-5, and IL-13. These cytokines activate B lymphocytes to secrete antigen-specific IgEs, which are released into the circulation and bind to mast cells residing in the airway mucosa. Renewed contact with the allergen results in cross-linking of the antigen with its specific mast cell-bound IgE, inducing mast cell degranulation with a local release of histamine, tryptase, and leukotrienes. These mediators act on the surrounding tissues, causing the acute allergic symptoms being sneezing, rhinorrhea, wheezing, coughing, and bronchoconstriction.

Low molecular weight agents are nonimmunogenic in their native state. However, some LMW agents are capable of sensitizing the adaptive immune system by acting as haptens, forming conjugates with proteins, such as keratin or albumin (19). These hapten–protein complexes are recognized by dendritic cells and, like HMW agents, presented to naive $CD4^+$ cells, which can initiate an immune response. However, the type of immune response that is generated can vary. For example, platinum salts and acid anhydrides are generally considered to induce rhinitis and asthma with the production of specific IgE antibodies, and therefore, skin prick test (SPT) with these agents can show a cutaneous hypersensitivity in

sensitized individuals (28). Other LMW agents, such as isocyanates, Western red cedar, and acrylates, probably do not act via specific IgE, even though they induce similar clinical symptoms (29). This might be related to the different ways hapten conjugates are processed by dendritic cells. When the conjugates are processed intracellularly, they are presented by MHC-I molecules and recognized by $CD8^+$ lymphocytes. However, when they escape endogenous processing, they are presented by MHC-II molecules to $CD4^+$ lymphocytes (30) that can develop into either a Th1 or Th2 subtype, leading to the production of their respective cytokines (IFN-γ for Th1; IL-4, IL-5 for Th2) and immunoglobulins (IgG for Th1; IgE for Th2). While previously it was suggested that Th1 and Th2 cytokines counterbalanced each other, it has become clear that in LMW sensitizer-induced disease, both Th1 and Th2 cytokines are involved (31). The resulting airway inflammatory process is similar for IgE- and non-IgE-inducing agents and is characterized by the presence of eosinophils, lymphocytes, neutrophils, mast cells, and features of airway remodeling (32, 33).

The adaptive immune system does not appear to be directly involved in airway inflammation caused by LMW irritant chemicals to which the host does not become sensitized. Irritants are more likely to interfere with the neurogenic or innate immune system of the airways.

Known effects of inhaled occupational agents on the neurogenic system

Sensory nerve fibers present underneath the airway epithelium express certain chemoreceptors, among which the transient receptor potential (TRP) channel family is the most important (Fig. 2). One of the most commonly expressed subtypes of TRP channels in the airways is the TRP ankyrin (A) 1 channel, which has emerged as a major irritant detector (34). It has been shown that TRPA1 is activated *in vitro* by irritants such as acrolein, tear gas, vehicle exhaust (35), ozone (36), hydrogen peroxide, and hypochlorite (37). *In vivo*, it was proven that noxious respiratory effects of styrene and naphthalene (38), as well as hypochlorite (37), are TRPA1 dependent. Therefore, TRPA1 is believed to play an important role in the pathophysiology of occupational airway disease.

Following the activation of these chemoreceptors on the sensory afferent nerve fibers, an orthodromic signal is generated via the central nervous system, leading to central reflexes like coughing. At the same time, the antidromic axon reflex leads to an immediate, local release of neuropeptides, such as substance P (SP) and neurokinins (39) (Fig. 2). These neuropeptides activate their receptors located on mucosal blood vessels, submucosal glands, and inflammatory cells (40), which results in the induction of upper respiratory symptoms such as rhinorrhea, nasal blockage, and sneezing.

Several data in the literature suggest a role of the neurogenic system in occupational airway disease and more specifically in irritant-induced symptoms, which are by definition activators of the trigeminal nerve endings (20). Scheerens et al. showed that *in vitro* application of toluene di-isocyanate (TDI) induces the release of SP in mouse isolated trachea (41). The finding of Meggs et al. that nasal biopsies of patients with RUDS after chlorine dioxide exposure showed an increased number of nerve fibers (22) can provide a possible explanation why a single irritant exposure can lead to persistent symptoms, even after the agent has disappeared.

Additionally, solitary chemoreceptor cells (SCCs) have been found scattered throughout the nasal epithelium (42)

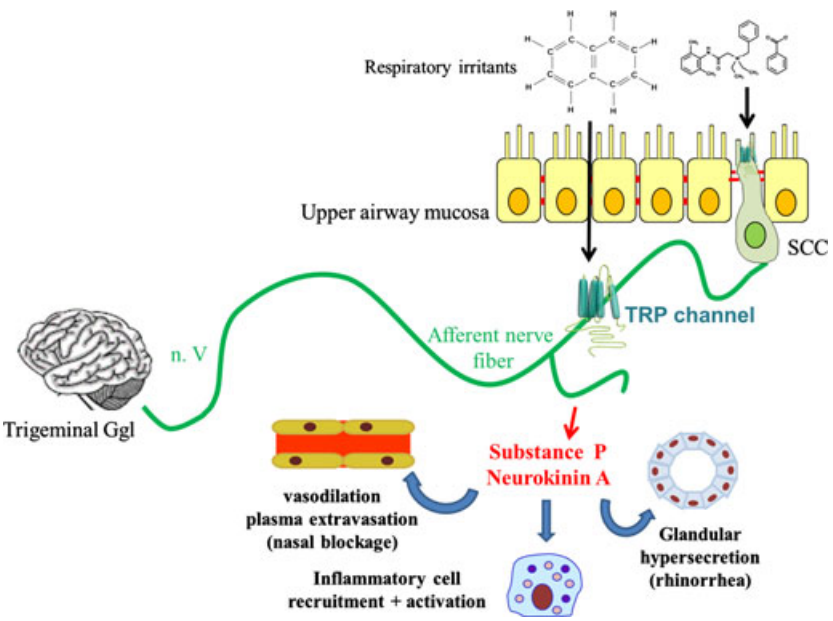

Figure 2 Role of the sensory nerves in occupational airway inflammation.

(Fig. 2). These cells also express chemoreceptors such as TRPM5 and bitter taste receptors, which are activated by specific respiratory irritants (43). Because these SCCs are directly contacted by sensory nerve endings, it is likely that activation of these cells has similar effects on the nervous system and the surrounding tissues.

Effects of inhaled occupational agents on the innate immune system

Unlike the adaptive immune system, the innate immune system responds immediately and in a nonspecific manner to environmental agents. The typical cells of the innate system are epithelial cells, natural killer (NK) cells, neutrophils, and eosinophils. Particularly in the case of RUDS, the respiratory epithelium is directly exposed to high amounts of irritant. This can lead to desquamation of epithelial cells and increased permeability of epithelial cell junctions (22).

Other innate responsive cells such as iNKT cells and γδT cells belong to the lymphocyte population, but are capable of responding immediately to exogenous stimuli and have been shown to be involved in certain mouse models of airway dysfunction induced by irritants such as chlorine gas and ozone (44, 45).

Mast cells, the main effector cells in classical allergies, also play a role in the innate immune response, not only because of their specific location within tissues that interface the external environment, but also because they express numerous receptors that are directly activated by exogenous agents. Some anecdotal clinical studies suggest a possible involvement of mast cells in occupational airway disease induced by LMW agents; mast cell numbers are decreased in bronchial mucosa after cessation of di-isocyanate exposure (46) and increased tryptase concentrations are seen in nasal lavages of patients suffering from glutaraldehyde-induced occupational rhinitis (47). *In vitro*, it has been shown that ammonium persulphate induces a direct degranulation of the LAD2 mast cell line (48) and that diesel exhaust particles (DEP) enhances FcεRI-induced degranulation in a murine mast cell line (49).

Animal models investigating occupational airway disease

Although differences exist between human and murine airway morphology, mouse models represent a powerful tool to unravel immunological and pathophysiological aspects of airway diseases. In comparison with airway allergies caused by HMW agents, there has been done very little experimental research using laboratory animals to investigate LMW-induced occupational asthma and rhinitis. Vanoirbeek et al. developed a mouse model of chemical-induced asthma, using the LMW sensitizers TDI and trimellitic anhydride (50, 51), characterized by airway hyperreactivity, airway inflammation, and an increased total serum IgE. In contrast to the typical eosinophilic HMW-induced allergy, these chemicals induce a more neutrophilic type of inflammation when sensitization occurs via the skin. The same mouse model was later also validated for ammonium persulphate (52). Johnson developed a mouse model of TDI-induced rhinitis via respiratory sensitization, which induced a more eosinophilic type of airway inflammation (53). Regarding antibody production, bronchial responses, and cytokine pattern, results were similar between the different models.

Little experimental *in vivo* research has been conducted to clarify the mechanisms of persistent nasal symptoms that occur after a single acute inhalation injury. Respiratory irritants all induce an immediate 'irritation response' in rodents characterized by a decreased respiratory frequency, which is mediated through the stimulation of the trigeminal nerve (20). Interestingly, Morris showed that this response to the irritants acrolein and acetic acid was enhanced in mice suffering from allergic airway disease (54), which can be considered a model of work-exacerbated rhinitis. Martin et al. described airway hyperreactivity in mice after a single inhalation of chlorine gas with epithelial damage in the lower airways, protein exudates, and influx of inflammatory cells (55). Further publications by the same group point to the involvement of γδT cells in the observed effects (44) and signs of airway remodeling at 10 days postexposure (45).

A small number of groups developed mouse models that explore the mechanisms by which low concentrations of irritants can influence airway function and immunology. The group of Diaz-Sanchez explored the effects of DEP exposure *in vivo*, showing their Th2 adjuvant activity when inhaled with conventional antigens (56) as well as the induction of IFN-γ production by NK and NKT cells (57). A mouse model of ozone-induced asthma has been set up by the group of Pichavant, in which the presence of iNKT cells and IL-17 seem to be crucial (58). Our group recently developed a mouse model of hypochlorite-induced airway disease, which shows the involvement of both the TRPA1 channel and mast cells in the induction of airway hyperreactivity (37, 59).

Diagnosis and management of occupational upper airway disease

Diagnosis

Diagnosing occupational upper airway disease is challenging for the clinician. The most important element is to think about the possibility of an occupational etiology in any patient suffering from chronic upper airway disease. Hence, it is important to take an appropriate history about the occurrence, type, and duration of upper airway symptoms in relation to work and to enquire about accidental exposures or spills. Symptoms of runny nose, nasal obstruction, sneezing, itch, and nose bleeds linked to specific exposures at work are suggestive for occupational rhinitis (4). Additional complaints of facial pressure, postnasal drip, and smell reduction are suggestive for progression toward rhinosinusitis. Additionally, it is important to be alert for an improvement of sinonasal symptoms during weekends and holidays.

However, given the high frequency of upper airway symptoms in the general population (60), objective tests confirming the occupational etiology are necessary for an appropriate management. The first step in establishing the work-related origin is the exclusion of other common causes

such as local factors (septal deviations, nasal valve dysfunction) or allergies to common allergens, for example house dust mite, pollens, molds, or pets. Another method is the 'work removal – work resumption test': The patient is assessed after a period of a few weeks away from the suspected exposure and is reassessed again a few weeks after work resumption.

When the work-related upper airway symptoms are linked to exposure to a HMW agent, sensitization can be detected by means of SPT or serum testing for specific IgEs. However, as described above, sensitization to LMW agents does not necessarily lead to a production of detectable specific IgEs, which makes it impossible to detect the causative LMW sensitizer by showing antigen-specific IgE.

Consequently, a causal relationship between exposure to a specific occupational agent and upper airway disease can only be established with certainty by specific nasal provocation testing (NPT) with the suspected agent (5). HMW agents can be directly administered to the nasal mucosa by means of a spray or dropper. Unfortunately, LMW agents are often water insoluble, and alternative administration methods for NPT have to be used. For this reason, the agent is often administered by mimicking the exposure conditions at the workplace (e.g., tray tipping, preparing reagents) in dedicated challenge rooms under close supervision and monitoring of the nasal response (61) by means of symptom scoring, visual analogue scales (VAS), nasal patency measurements (rhinomanometry, peak nasal inspiratory flow), and assessment of volume and inflammatory composition of nasal secretions.

The available studies on NPT in occupational rhinitis induced by LMW agents are extremely scarce. The group of Toskala published on NPTs performed in 165 suspected occupational rhinitis patients, but mainly HMW agents were tested (62). About 50% of the NPTs with wood dust were positive; the other LMW agents tested did not yield a positive response. Desrosiers et al. found a significant response in terms of nasal symptoms, patency, and inflammation in seven patients undergoing a provocation with isocyanates (63). Moscato published a series of 47 hairdressers undergoing NPT with ammonium persulphate. However, all these studies lacked a control group. Diab demonstrated that hairdressers with persulphate-associated rhinitis showed both an early and a late response to NPT with persulphates in terms of symptoms, nasal patency, and inflammatory markers, in contrast with nonsymptomatic hairdressers (64). Interestingly, patients with atopic rhinitis also showed an early response to persulphate provocations, suggesting a nonspecific early response to the agent.

Evaluation of nasal inflammatory profile is an important component in NPT and can provide an additional objective tool in determining the causal relationship between occupational agent and nasal symptoms. The inflammatory cell profile is assessed by performing a nasal brushing/scraping, a nasal lavage (65), or collecting blown secretions (66). In addition, nasal inflammatory markers can be determined on nasal lavage fluid or – especially when less abundant mediators are involved – by using nasal tampons (65). Again, most evidence on nasal inflammation assessment is available for NPT in rhinitis caused by HMW agents, characterized by an eosinophilic inflammation with the release of related mediators (e.g., eosinophil cationic protein), in the nasal mucosa (67). However, anecdotal studies report on NPT in patients suffering from LMW-induced occupational rhinitis, which lead to an inflammatory cell recruitment to the nasal mucosa. As discussed previously, mechanisms of LMW-induced upper airway disease vary substantially and so do inflammatory cells and mediators that have been demonstrated to be associated with exposure: eosinophils (68), neutrophils and myeloperoxidase (69), IL-8 (70), tryptase (71), and more general pro-inflammatory markers (72).

Although nasal nitric oxide levels have been shown to be increased in patients with rhinitis, both in the nonoccupational (73) and in the occupational setting (72), standardization of this test is currently insufficient to be used as a determinant of NPT to prove the relationship between a specific occupational agent and upper airway symptoms.

Unlike provocation testing for occupational asthma, no specific cutoff values for changes in nasal patency, secretory activity, or symptoms have been proposed to define a positive reaction, but guidelines for performing NPT have been published in the 2009 EAACI position paper on occupational rhinitis (5). Figure 3 depicts a flowchart for diagnosing the chronic upper airway patient with positive occupational history, adapted from the one published in this position paper. It includes NPT in case of suspected LMW agents or for suspected HMW-induced occupational rhinitis despite negative immunological testing. If NPT remains negative, but the clinical history is highly suggestive for work-related disease or when NPT is not feasible, a workplace assessment of upper airway symptoms in combination with clinical testing can still lead to the diagnosis of occupational airway disease.

Management

The initial step in managing occupational airway disease is prevention of its development by appropriate occupational hygiene including observance of exposure standards and surveillance of employees in high-risk work environments. Early symptoms or sensitizations can be picked up by means of questionnaires, SPT for specific agents, and increased awareness for onset of nasal symptoms with referral if needed (74). Once occupational work-related upper airway symptoms are established, avoidance of or reduction in exposure to the suspected causal agent is the key feature of the treatment strategy. Although studies are scarce, it has been shown in patients suffering from occupational rhinitis to latex or biological enzymes that reduction in occupational exposure successfully decreased occupational rhinitis symptoms (75, 76). Reduced exposure can be achieved by improving ventilation systems, wearing appropriate protective clothing and masks, and, if possible, relocation of the patient to another job without exposure.

When adequate reduction in exposure is impossible or insufficient, rhinitis or rhinosinusitis should be treated according to the guidelines for nonoccupational upper airway disease. In case of HMW agents, ARIA guidelines for the

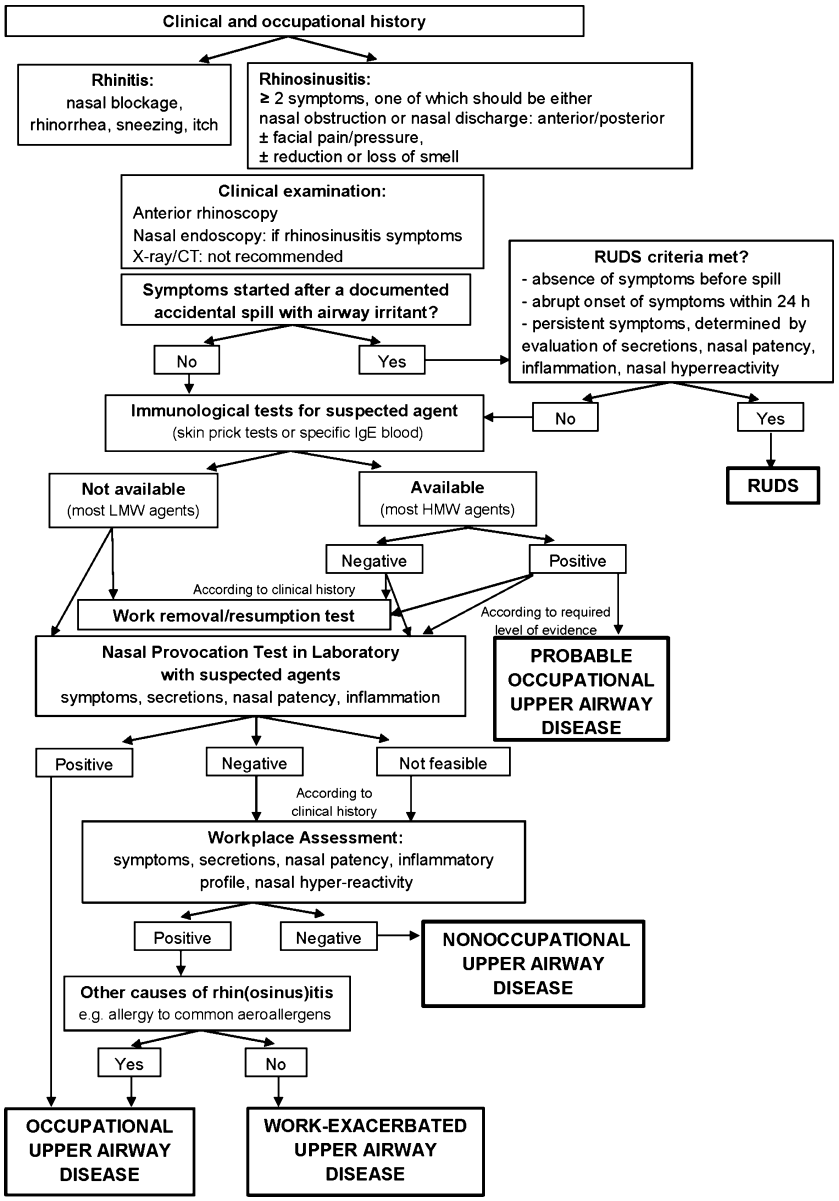

Figure 3 Diagnostic flowchart for the upper airway disease patient with positive occupational history. HMW, high molecular weight; LMW, low molecular weight; RUDS, reactive upper airway dysfunction syndrome.

treatment of allergic rhinitis are indicated with the use of topical steroids and/or antihistamines (1). When clinical presentation meets the criteria for rhinosinusitis (presence of two or more sinonasal symptoms – being nasal blockage, nasal discharge, facial pain, and/or smell impairment – in combination with either endoscopic signs or CT changes), patients should be treated according to the EPOS guidelines (2). Currently, there is no evidence for the beneficial effects of immunotherapy in occupational upper airway disease.

Because it is clear that patients suffering from occupational upper airway disease are at higher risk of developing occupational asthma, a close follow-up with awareness for the induction of lower airway symptoms and, if necessary, lung function testing are required (5).

Unmet needs in the field of occupational upper airway disease

Due to the lack of validated diagnostic tests and epidemiological studies, the incidence of occupational rhinitis is considerably underestimated and hardly anything is known about the occurrence of occupational rhinosinusitis. In order to get a proper insight into the prevalence and severity of these diseases, population-based studies are required to map

the occurrence and risk factors for work-related upper airway disease.

Secondly, an early diagnosis of this disease is of great medical importance as occupational rhinitis may progress into occupational asthma (7), or possibly rhinosinusitis, following prolonged exposure to the causative agents. However, adequate diagnostic procedures such as NPT are only applied by a limited amount of clinical centers and remain poorly standardized. This finding should lead to early detection of lower airway problems before patients reach a point of irreversible bronchial disease.

In the case of work-aggravated rhin(osinus)itis, in which occupational exposure plays a role in maintaining or aggravating pre-existing rhin(osinus)itis (5), awareness of potential harmful work-related exposures is of importance in evaluating treatment strategies of nonoccupational upper airway symptoms, because it can lead to the wrong conclusion of therapy-resistant disease (77). However in some cases, removal of the patient from his work environment might improve his upper airway symptoms.

Finally, data on pathophysiological mechanisms of the majority of occupational agents are currently lacking. Besides the classical 'irritant response', the effects of most of the work-related LMW agents on airway immunology and function remain largely unknown. Because the burden of occupational agents is increasing, the number of potentially harmful substances rises simultaneously and it is likely that products which are initially believed to be harmless might form an unexpected risk to the airways.

Further research in the field should focus on the remaining gaps in our knowledge being (i) mechanisms of action of irritants (not only single chemicals, but also complex mixtures such as DEP, fire smoke, and plastic fumes) at the cellular level; (ii) relationships between occupational dermatitis and airway disease; and (iii) possible predictors of progression of occupational rhinitis to rhinosinusitis and/or asthma.

After improving our insight into the latter crucial aspects of the pathophysiology of occupational airway disease, we will be capable of improving our current approach toward patients with occupational airway disease.

Conclusion

Chronic upper airway disease is one of the most prevalent diseases in the developing countries. Although there is evidence for occupational agents being involved in a subgroup, little research has been performed on the prevalence of occupational upper airway disease and the possible harmful effects of some of the substances used at the work floor. The disease remains underdiagnosed due to the complexity and time-consuming nature of diagnosis in a subgroup of patients. However, when patients suffering from occupational upper airway disease avoid exposure to the causal agent, a significant improvement in general health, professional productivity, and quality of life can be expected, in parallel with an arrest on the progression toward occupational asthma.

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Author contributions

VH was involved in the intellectual contribution, literature search, and drafting and writing of the article. BS, WF, BN, and PH were involved in the intellectual contribution, writing and revising of the article.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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