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Occupational Rhinitis and Asthma: Where Do We Stand, Where Do We Go?

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Abstract This review provides an overview of current and emerging issues regarding occupational rhinitis (OR) and occupational asthma (OA), focusing on studies discussing concepts and results that are relevant to both diseases. OA and OR are conditions that affect the upper and lower airways, are characterized by reduced airway caliber and hyperresponsiveness and by inflammation, and are caused by agents present in the workplace. To explain disease expression, research is moving from the T-helper type 1/type 2 cells paradigm to consider the contribution of diverse alternative pathways such as neural inflammation, a dysfunctional epithelial barrier, and autoimmune mechanisms, among others. Objective assessment of OR and OA has been improved and tested for research and, currently, clinical application. Further developments in the field of OR are expected to lead to more generalized clinical applications, following the example of what has been achieved for OA.

Keywords Rhinitis · Asthma · Occupational · Pathogenesis · Risk factors · Diagnosis · Outcomes

Introduction

Workers are exposed at work to a range of allergens and chemicals with the potential to cause diverse respiratory illnesses. As shown in Fig. 1, this exposure may be associated with a wide spectrum of conditions ranging from irritation of airway mucus membranes to aggravation of preexisting rhinitis and asthma and to clinically established occupational rhinitis (OR) and occupational asthma (OA).

General reviews were published on the topics of OA and OR in 2008 and 2009 [1••, 2••, 3]. The purpose of this publication is to review key articles that were issued during this period with a view toward updating findings thought to represent knowledge gaps pertaining to these diseases. This article is made up of three major sections: the first addresses some common issues related to OR and OA, while the second and the third focus on OR and OA, respectively.

Nosology of Occupational Rhinitis and Asthma

Guidelines on core aspects of OR, such as definition and classification, clinical presentation, diagnosis, and management, were recently issued [1••]. OR is classified into two groups: allergic (including IgE-mediated and non–IgE-mediated types) and nonallergic (irritant-induced type). As presented, the clinical spectrum of OR and OA comprises distinct phenotypes, and nasal and bronchial symptoms may result from immunologic and nonimmunologic mechanisms that have not been fully elucidated.

Two types of OA exist: one that occurs after a latency period that is necessary in becoming "allergic" and in which a sensitizing process can be identified or suspected, and the other that occurs without a latency period, after an inhalation accident. The latter condition is also known as *reactive airways dysfunction syndrome* (RADS) [2••].

Endophenotyping Occupational Rhinitis and Asthma

OR and OA fall into the category of complex diseases. Thus, in their pathogenesis, a multifaceted interaction

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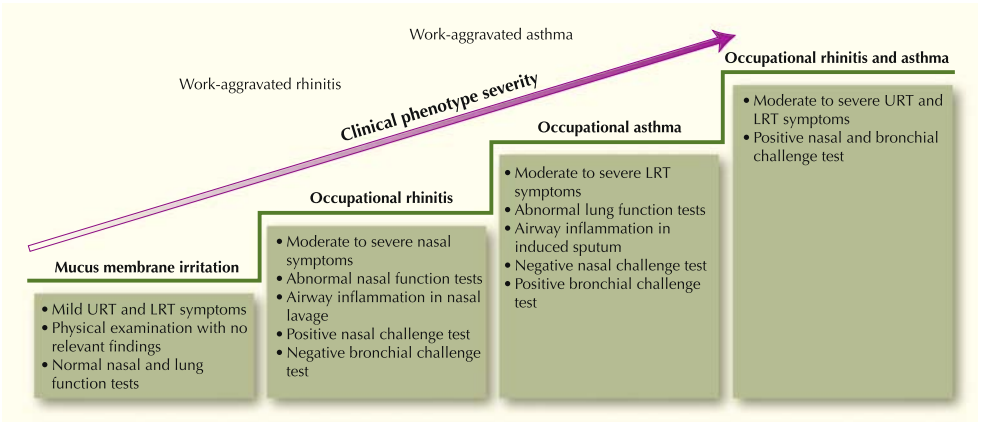

Fig. 1 Clinical spectrum of work-related rhinitis and asthma as a function of severity of clinical manifestations. The main clinical features are shown for occupational rhinitis and occupational asthma. Work-aggravated rhinitis and asthma denote preexisting disease not attributable to specific work exposure. LRT—lower respiratory tract; URT—upper respiratory tract

between diverse genetic and environmental factors is expected to occur. The term *phenotype* represents all the observable characteristics of an organism. OR and OA are both heterogeneous diseases consisting of two major types and several potential subtypes based on clinical presentation. The term *endophenotype*, which originally emerged from the psychiatric literature, is used to describe an internal, nonobservable phenotype acting as an intermediary between the disease and the gene [4]. This is in contrast to the conventional thinking on disease causal pathway leading directly from gene to disease. As depicted in Fig. 2, the ultimate disease expression, or phenotype, is then regarded as the outcome of multiple genetically influenced endophenotypes interacting with environmental and epigenetic factors. In the context of the asthma literature, Anderson [5•] recently proposed the term *endotype* (contraction of endophenotype) to denote "a subtype of disease defined functionally and pathologically by a molecular mechanism or by treatment response" [5•]. An endophenotype investigative approach would be more advantageous in identifying relevant phenotypes associated with OR and OA because a particular endophenotype is expected to be affected by fewer genes than phenotypes themselves [4]. This approach thus may serve not only to better define and classify OR and OA but also to identify genes and pathogenic pathways leading to the disease by creating homogeneous subgroups of patients according to endophenotypic features [4].

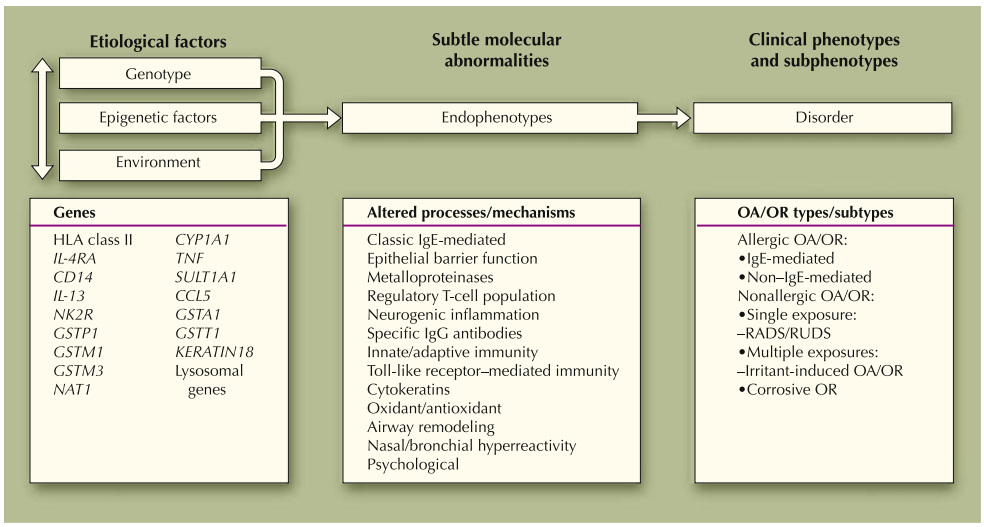

Fig. 2 Endophenotype approach to investigate genetics and pathogenesis of disease with application to occupational asthma (OA) and rhinitis (OR). The figure depicts a path to disease with endophenotypes as intermediate between gene and phenotypes. It also depicts potential interactions between genes and environmental and epigenetic factors. Genes in the first list are potential candidates genes for association with OA reported in human and animal studies (with most studies investigating diisocyanates-induced OA). This is not a definitive and exhaustive list of genes. The same applies for the list of processes/mechanisms. It only shows candidate biological pathways to investigate endophenotypes that may lead to identification and defining of particular phenotypes and subphenotypes of OR and OA. The list of OR/OA types/subtypes displays the current accepted classifications of OR and OA. To learn about gene names and functions, the reader is referred to the Online Mendelian Inheritance in Man database. IL—interleukin; RADS—reactive airways dysfunction syndrome; RUDS—reactive upper airways dysfunction syndrome; TNF—tumor necrosis factor

Pathogenic Aspects of Occupational Rhinitis and Asthma

Mechanistic studies aiming specifically to elucidate pathogenic aspects and the genetic basis of OR are scarce. However, considering the "united airways" concept that links rhinitis and asthma in the general population [6] and in the workplace [7•], it is believed that OR and OA share pathogenic mechanisms; thus, OA research may advance knowledge on OR pathogenesis and vice versa.

Genetic susceptibility to occupational diseases was discussed with special consideration given to OA caused by diisocyanates. HLA susceptibility has been examined in different studies with discrepant results in terms of associated protective or favoring polymorphisms [8]. Lysosomal genes and genes involved in glutathione S-transferase, N-acetyltransferase, and neurokinin pathways also have been investigated [8].

Sensory Nerves: A Critical Role in Occupational Rhinitis?

Nonallergic neural mechanisms may play a significant role in the pathogenesis of OR via induction of neurogenic inflammation [9]. The exact mechanisms involved are unknown, but neurotrophins are thought to play a crucial role. Neurotrophins such as the nerve growth factor upregulate the synthesis and release of multiple sensory neuropeptides, including structurally related tachykinins such as substance P, neurokinin A and neurokinin B, and calcitonin gene-related peptide [10]. These neuropeptides can be recovered from the airways as the result of a variety of stimuli, including ozone, cigarette smoke, capsaicin, ether, low pH, isocyanates, and allergens [11]. Their biological effects play a major role in the initiation of neurogenic inflammation inducing edema and vasodilatation, which may be clinically associated with nasal obstruction in the upper airway. Besides, tachykinins also have important immunomodulatory effects influencing inflammatory cells [10]. All the above observations strongly suggest a potential role for neurotrophins and tachykinins in the pathogenesis of OR. However, no studies have examined the specific role of these mediators in the causation of this disease. Moreover, it is important to define their role according to the specific type of OR.

Allergen Sensitization in Occupational Asthma and Occupational Rhinitis: An Ever-Controversial Role

It is well-established that specific IgE antibodies cannot be demonstrated in all workers affected by OA and OR caused by high and low molecular weight agents. A murine model of baker's asthma failed to sensitize mice and to demonstrate an eosinophilic inflammatory response after challenge with flour allergens. However, after successive challenges, a proinflammatory response demonstrated by enhanced neutrophilic inflammation was observed. This suggests that pathogenic pathways not necessarily associated with allergen sensitization may contribute to generating work-related asthma and rhinitis symptoms [12].

A discrepancy between allergen sensitization and rhinitis symptoms was demonstrated in differentially exposed laboratory animal workers [13]. Among directly exposed workers, 32% reported work-related symptoms, with only 11% showing sensitization to laboratory animal allergens. In contrast, symptoms were only reported by 9 of 27 patients with demonstrable sensitization. A longitudinal study corroborated the above observation. A study carried out among 114 Danish baker apprentices over 20 months showed that although the incidence of nasal and respiratory symptoms was high, the cumulative incidence of occupational sensitization was low (6.1%) [14].

The lack of correspondence between allergen sensitization and clinical expression of rhinitis and asthma symptoms may be explained by other reasons, including false-negative results originating from differences in antigen composition and concentration in extracts used in diagnostic tests and methods [8]. A recent study showed sensitization to water-insoluble allergens belonging to the wheat gliadins family in bakers with OA, some of whom had tested negative on a standard IgE test for wheat extract [15]. Some specific proteins associated with sensitization also have been described in snow crab processors [16].

A pathogenic pathway involving local IgE production is an attractive potential endophenotype to explain the occurrence of clinical disease without demonstrable allergen-specific IgE [17]. A major implication for clinical practice is that nasal and bronchial challenge tests may be crucial for diagnostic purposes in symptomatic patients with negative skin prick tests, and in the absence of systemic allergen-specific IgE [18]. Nevertheless, clinical studies demonstrate the utility of allergen-specific IgE and skin prick tests when evaluating symptomatic individuals through specific nasal and/or bronchial challenge test. High serum levels of flour-specific IgE and confirmed positive skin prick test results for flour extract were shown to be good predictors of a positive challenge test in 107 bakers [19]. Based on this observation, investigators suggest that challenge tests may not always be necessary in cases displaying a clear skin prick test and serologically specific IgE response.

Lessons From Animal Models

An interesting study using a murine model of toluene diisocyanate (TDI)–induced rhinitis showed that mice exposed to TDI vapors displayed characteristics of allergic rhinitis seen in humans [20•]. TDI inhalation induced

eosinophilic nasal mucosa inflammation and an increased expression of the nasal mucosa of inflammatory mediators indicative of a T-helper type 1/type 2 immunologic response. These changes corresponded to changes in breathing parameters, increases in IgE, and TDI-specific IgG antibodies in the serum. Interestingly, the model failed to demonstrate associated changes in the lungs, suggesting an immune/inflammatory response restricted to the upper airways.

A similar experimental murine model of TDI-induced asthma assessed changes over time in functional and inflammatory parameters, systemic indicators of sensitization, and lymphocyte cell subpopulations recovered from local lymph nodes [21]. This study showed persistence of systemic sensitization up to 90 days after initial sensitization, increased release of interleukin-4 and interferon-γ in auricular lymph nodes up to 20 days following sensitization, and increased methacholine reactivity as well as increased neutrophilic inflammation and macrophage inflammatory protein 2 in bronchoalveolar lavage fluid up to 50 days following TDI challenge.

All types of diisocyanates presumably may induce OA through a similar—if not the same—pathogenic pathway. TDI-induced asthma studies have suggested a more predominant role for neutrophils in observed airway inflammation. However, a recent study concluded that eosinophil activation may play a key role in asthma induced by methylene diphenyl diisocyanate [22]. This indicates that different endophenotypes may have a role in diisocyanate-induced OA.

Occupational Rhinitis

Frequency and Risk Factors

Construction painting workers showed a higher risk of asthma (odds ratio, 4.7; 95% CI, 1.4–16.1) and rhinitis symptoms (odds ratio, 2.4; 95% CI, 1.1–5.2) than carpenters not involved in painting [23]. The association between exposure to liquid detergent enzymes and upper and lower airway symptoms was examined in a cross-sectional study of 108 differentially exposed workers. Highly exposed detergent workers reported significantly more nasal symptoms and marginally significant more wheezing than the least exposed group [24].

Rhinitis symptoms were common among workers exposed to metalworking fluids in an automobile parts manufacturing plant (115 of 187, 61.5%) [25]. Pesticides seemed to be associated with rhinitis in an assembled cohort of 2245 commercial pesticide applicators. At least one episode of rhinitis in the past year was reported by 74% of the participants. Five pesticides (2,4-D, glyphosate, petroleum oil, diazinon, and benomyl) were significantly associated with rhinitis in the past year [26]. The precise pathogenic mechanisms of pesticide-induced rhinitis remain to be discussed.

Rhinitis symptoms are frequently reported by people living or working in water-damaged buildings in which exposure to molds is highly likely. This type of exposure may be associated with the development of sensitization and OR. Rhinitis symptoms were common among museum workers (71 of 103, 68.9%) and associated with allergy to molds in 30% of the study participants [27]. A series of OR cases caused by molds was reported; the diagnosis was based on a history of work-related nasal symptoms, workplace exposure assessment, and clinical investigations, and in all cases included performing nasal challenge tests with fungal allergens [28].

Occupational Rhinitis and Asthma Comorbidity

OR and OA often coexist, with OR being more common than OA [1••]. However, a recent study found that OR was reported one tenth as often in sentinel-based registers [29]. The coexistence of rhinitis and asthma in the workplace also has been investigated using the currently recommended diagnostic approach [1••]. In a published series of inhalation challenge tests using occupational agents (n = 1229), 10% of challenge investigations were positive and thus suggested OR. A concomitant asthmatic reaction was observed in 13% of the challenges [30]. Another study used challenge test methodology to evaluate 43 individuals presenting with histories suggestive of OA and at the same time reporting work-related rhinitis symptoms. A positive nasal challenge was observed in 25 of 43 investigations (58%), whereas a positive bronchial challenge was observed in 17 of 43 (39.5%). Positive nasal and bronchial challenges indicative of OR and OA in the same patient were documented in 13 of 43 challenges (30.2%); OR occurred in 76.4% of confirmed cases of OA [7•]. Data from these studies provide evidence of the link between OR and OA and highlight the importance of assessing rhinitis in patients complaining of work-related asthma symptoms.

Finally, epidemiologic data from national reporting schemes provide another way to examine the association between OR and OA as well as to establish the relative frequency with which various families of agents cause rhinitis or asthma [31]. Toxicokinetic factors may account for the observation of a higher frequency of rhinitis associated with exposure to sensitizers acting through known IgE-mediated mechanisms [29].

Diagnostic Means and Treatment

Methods to investigate upper airway inflammation have been tested in the context of inhalation challenge test with

occupational agents [32, 33]. The clinical diagnostic value of monitoring nasal inflammation for the diagnosis of OR requires more research.

The pharmacologic management of OR and OA does not differ from that offered to patients with nonoccupational rhinitis and asthma. There is a consensus that airway eosinophilia plays a key role in allergic occupational and nonoccupational rhinitis and asthma. Interestingly, a recent animal study demonstrated the capability of a live vaccine strain to suppress airway eosinophilia and lung pathology using a murine model of allergic disease [34]. This constitutes a potential novel treatment avenue that should be explored further.

Outcomes of Occupational Rhinitis

Only recently have studies investigating the long-term outcomes of OR started to emerge. Health-related quality of life was assessed 10 years after confirmation of diagnosis of OR and was found to be impaired among patients with continued exposure compared with those who were no longer exposed [35]. Further research is needed to corroborate these findings and to assess the histopathologic, socioeconomic, and clinical consequences of OR.

Occupational Asthma

Frequency and Risk Factors

The frequency of OA has been assessed in meta-analyses, sentinel-based projects, population-based studies in general registers, and in cross-sectional and longitudinal studies. Toren and Blanc [36] reassessed the frequency of OA using a meta-analytic approach they originally proposed in 1999 in a frequently cited paper. They found an overall median population-attributable risk of 17.6%, a figure comparable to what they found in their previous estimate. The sentinel-based Shield surveillance scheme, initiated in the Midlands of the United Kingdom 15 years ago, showed that metal fluid is frequently emerging as a new potential cause of OA, while diisocyanates remain the most common causal agent [37]. The trend to compensate for OA due to latex has steadily declined since 1990 in Belgium, this being associated with a reduction in the use of powdered gloves (with the powder representing a vehicle for dispersion of latex particles) [38]. A literature review spanning the years 1980 to 2006 suggests a reduction in the prevalence of OA due to laboratory animals [39]. Finally, a population-based study carried out in Montreal showed that airway hyperresponsiveness was associated with exposure to occupational sensitizers, with a population-attributable risk of 31% [40].

A prospective study in 385 apprentice car painters assessed changes over 18 months in specific antibodies to hexamethylene diisocyanates and the incidence of work-related respiratory symptoms associated with these changes. At follow-up, the incidence proportion of work-related lower and upper airway symptoms was 4.4% and 6.4%, respectively. A small proportion of participants showed increases in hexamethylene diisocyanate–specific IgG and IgE; increases in specific IgG and IgG_4 seemed to have a protective effect against the incidence of respiratory symptoms [41].

The results of several prevalence studies of OA in various workplaces have been published. Although symptoms are common among bakers, relatively low prevalence figures of 4.5% for IgE-mediated sensitization and 1.5% for OA were found by Hur and coworkers [42] in South Korea. Many studies have shown that the prevalence of asthma in cleaners is higher than that of the general population, a finding extended to nondomestic cleaners in a cross-sectional study carried out in Ontario [43]. Arif and coworkers [44] found that asthma was significantly more common not only among nurses who had been exposed to latex in the previous years, but also among those using various disinfectants.

Using data collected in prospective studies of various apprentices exposed to high and low molecular weight agents, Suarthana and coworkers [45] found that the use of skin prick testing with animal-derived allergens added little to questionnaires in terms of their capability of predicting incident work-related sensitization and symptoms, and also that the use of a job exposure matrix seemed satisfactory in estimating the risk of various outcomes of occupational allergies but ideally should be complemented by an exposure verification [46].

Incidence studies are uncommon in the field of OA. Apprentices represent an ideal population for the assessment of the natural history of OA from the outset of exposure. Gautrin and coworkers [47••] examined the long-term (8-year) incidence of sensitization and nasoconjunctival and respiratory symptoms in a cohort of 408 individuals exposed to high molecular weight agents (animals, latex, flour, and enzymes). These individuals were previously assessed at the beginning and the end of their apprenticeship program. Focusing their analysis on the 78% of participants who were still exposed to the occupational allergen, they found a much lower incidence of symptoms and sensitization since the beginning of employment than during the apprenticeship period. The authors identified many personal factors that were significantly associated with a loss of sensitization and symptoms in those no longer exposed or with the onset of sensitization and symptoms in those who continued to be exposed [47••].

Clinical Aspects

Although many consensus practice guidelines on diagnostic procedures have been issued and made widely available

over the years—the latest addition being the British Thoracic Society initiative [48••]—they are still insufficiently applied, as shown by audits in Finland [49]. Serial assessment of peak expiratory flows comparing periods at work and away from work has been advocated since 1980 because this approach is superior to two single cross-shift assessments of spirometry (as was recently reconfirmed) [50]. A minimum of 8 working days and 3 rest days of 2-hourly assessments is required [51]. In the case of diisocyanates, the level of specific IgG or IgE antibodies is not sufficiently associated with diagnosis for it to be used on a clinical basis [52]. Exposure of workers to the agent suspected of causing OA can be carried out in a hospital laboratory or in the workplace, which is a useful adjunct to the investigation means. Assessment of airway inflammation with exhaled nitric oxide also seems to represent a useful addition to the diagnostic arsenal [53].

Finally, many new causes of OA have been published as case reports. For an annual update of all agents identified as causes of OA, the interested reader is referred to the following website: http://www.asthme.csst.qc.ca.

Prevention, Outcomes, and Cost

An interesting review was published on key aspects of primary prevention of OA, including the establishment of consistent criteria for the identification of at-risk agents, publication of a list of occupational asthmagens, and the requirement for inhalation protection [54]. Although reducing exposure is a key aspect of prevention, this is questionable once a worker has developed OA and a return to work is being considered [55]. Implementation of a powder-free natural rubber latex program in Germany improved symptoms and quality of life among health care workers who were allergic to latex, although many workers still experienced persistent symptoms [56]. Individuals with OA are generally left with significant psychological distress, as reviewed by Lavoie and coworkers [57]. Costs of OA were assessed in workers compensated for OA from 1988 to 2002 in Quebec. Mean costs were $75,000 (Canadian) and were significantly higher in older workers, men, those with more severe asthma at the time of diagnosis, and in cases of OA caused by low molecular weight agents [58].

RADS is a special form of OA that occurs in workers at risk of inhalation accidents. Malo and coworkers [59•] reported on the long-term outcomes of RADS. By reassessing 35 workers with RADS at a mean interval of 14 years after an inhalation accident, these authors showed that only six (17%) had normal responsiveness to methacholine, with more than two thirds of individuals still needing inhaled steroids to control their asthma symptoms. There was also an important impact on psychological outcomes. In addition, this group of researchers examined bronchial biopsies and lavage in a subset of 10 workers. Persistent eosinophilic inflammation was demonstrated; individuals with RADS also had increased remodelling shown by more basement membrane thickening than that observed in those with OA induced by sensitization [59•, 60].

Conclusions

The past few years have witnessed increasing and sustained research on OR and OA. The association between OR and OA is now better understood, and it seems from studies that they have more similarities than differences. Despite extensive research developments in the field, many issues remain elusive, especially with regard to their pathogenesis. Recent discoveries from animal and human studies and from growing research on the genetic basis of OA suggest a complex interplay among genetic factors, environmental exposures, and diverse stochastic events as the trigger for conditions such as OA and OR. Unravelling the pathogenesis of these common and disabling respiratory conditions requires a better definition of disease phenotypes; this may be useful not only to conceive novel diagnostic and therapeutic approaches but also to improve existing ones.

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- •• Of major importance

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