When to suspect occupational asthma

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C Lemière. When to suspect occupational asthma. Can Respir J 2013;20(6):442-444.

Occupational asthma (OA) is a difficult diagnosis to make. The present review describes the work environments in which workers are at risk for developing OA, the characteristics of the individuals in whom OA should be suspected and the investigation that can be performed to diagnose the condition. Accurately diagnosing OA is crucial because of the major social and economic consequences of this diagnosis on the patient.

Key Words: *Diagnosis of occupational asthma; Occupational asthma; Risk factors for occupatinal asthma*

Quand soupçonner un asthme professionnel

L'asthme professionnel (AP) est difficile à diagnostiquer. La présente analyse décrit les milieux de travail dans lesquels les travailleurs sont à risque d'AP, les caractéristiques des personnes chez qui on devrait soupçonner un AP et les examens à effectuer pour diagnostiquer le problème. Il est essentiel de bien diagnostiquer l'AP en raison des conséquences sociales et économiques considérables de ce diagnostic sur le patient.

Asthma is a common and costly chronic respiratory condition that affects >2 million Canadians ≥12 years of age (1). A systematic review of general population-based studies from various parts of the world published up to 2007 estimated that 17.6% of adult-onset asthma was attributable to workplace exposures (2). Asthma is considered to be 'work related' when there is a relationship between the symptoms of asthma and the workplace. Work-related asthma encompasses occupational asthma (OA) and work-exacerbated asthma (3). OA refers to de novo asthma or the recurrence of previously quiescent asthma (ie, asthma as a child or in the distant past that has been in remission) induced by either sensitization to a specific substance, which is termed 'sensitizer-induced OA', or by exposure to an inhaled irritant at work, which is termed 'irritant-induced OA'. Work-exacerbated asthma refers to asthma triggered by various work-related factors (eg, aeroallergens, irritants or exercise) in workers who are known to have pre-existing or concurrent asthma (ie, asthma that is occurring at the same time, but is not caused by workplace exposures) (3).

Detailed guidelines regarding the management of work-related asthma were published by a European Respiratory Society Task Force in 2012 (4). The aim of the present review was to focus on sensitizer-induced OA by describing the work environment and the clinical characteristics that may lead one to suspect sensitizer-induced OA in a worker with asthma; and summarizing the investigation that can be performed to diagnose sensitizer-induced OA.

WORKPLACES AND OCCUPATIONAL AGENTS ASSOCIATED WITH THE DEVELOPMENT OF OA

A very large number (>400) of substances used in the workplace can precipitate the development of sensitizer-induced OA (5). They are usually categorized into high-molecular-weight (HMW) and low-molecular-weight (LMW) agents (Table 1). HMW agents are proteins of plant and animal origin, while LMW agents include chemicals, metals and wood dusts. Although several hundred agents have been described to cause OA, only a handful (ie, flour, diisocyanates, latex, persulphate salts, aldehydes, animals, wood dusts, metals and enzymes) usually account for the majority (50% to 90%) of reported cases of OA (6,7). The distribution of causal agents may vary widely across geographical areas depending on the pattern of industrial activity (6,8-13). The highest incidence rates of OA occur in bakers and pastry makers, other food processors, spray painters, hairdressers, wood workers, health care workers, cleaners, farmers, laboratory technicians and welders. The substances to which the worker is potentially exposed to at work can be verified against a comprehensive list of

TABLE 1
Examples of occupations and agents responsible of sensitizer-induced occupational asthma

Occupation/industry	Agent	Molecular weight
Flour mills, bakers, pastry makers	Cereals, flour (wheat, rye, barley, buckwheat)	High
Health care workers, laboratory technicians	Latex	High
Laboratory workers, farmers, sea food processing	Animals (mice, rats, cows, sea food)	High
Baking product production, bakers, detergent production, pharmaceutical industry, food industry, health care workers	Enzymes (a-amylase, maxatase, alcalase, papain, bromelain, pancreatin, subtilisin)	High
Polyurethane production, plastic industry, insulation, molding, spray painting	Diisocyanates (toluene diisocyanate, methylene diphenyl-diisocyanate, hexamethylene diisocyanate)	Low
Metal refinery, metal alloy production, electroplating, welding	Metals (chromium, nickel, cobalt, platinum)	Low
Health care workers, cleaners	Biocides (formaldehyde, glutaraldehyde, quaternary ammonium compounds)	Low
Adhesives, dental and orthopedic materials, sculptured fingernails, printing inks, paints and coatings	Acrylates (cyanoacrylates, methacrylates, di- and triacrylates)	Low
Hairdressers	Hair bleaching (persulfate salts), hair dyes (paraphenylenediamine)	Low
Epoxy resin workers	Acid anhydride (phthalic, trimellitic, maleic, tetrachlorophthalic anhydrides)	Low
Textile workers, food industry workers	Reactive dyes (reactive black 5, pyrazolone derivatives, vinyl sulphones, carmine)	Low
Sawmill workers, carpenters, cabinet and furniture makers	Wood dust (red cedar, iroko, obeche, oak and others)	Low

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agents recognized to cause OA and the individual's employment can be searched on a list of at-risk occupations (3). Material safety data sheets can be requested from the workplace and may be of help in clarifying the presence of a workplace sensitizer. If the content of the causal agent is <1%, it may not be listed in the material safety data sheet. If available, the occupational health record and the industrial hygiene record from the company should also be reviewed. A comprehensive list of agents responsible for OA, as well as a list of occupations in which the exposure to those agents is encountered, can be found at <www.asthme.csst.qc.ca/info_med/index.html>.

HOST-RELATED FACTORS PREDISPOSING TO THE DEVELOPMENT OF SENSITIZER-INDUCED OA

As much as 20% of all cases of adult-onset asthma are due to occupational exposure. The precise factors that contribute to the development of OA in some, but not all, exposed individuals remain unknown. Various host markers have been implicated.

Atopy has been shown to be associated with sensitization to HMW agents in individuals with OA. For example, atopy was one of the main determinants for a specific sensitization to rodents in apprentices working in animal facilities (14) as well as for sensitization to latex in apprentices in dental hygiene (15). Pre-exposure sensitization to common allergens that are structurally similar to workplace allergens, such as pets of laboratory animal workers, could be a stronger risk factor for OA than atopy.

Smoking may also play a role in association with atopy in the risk for developing OA to some specific agents such as laboratory animals (16) and tetrachlorophtalic anhydride (17). However, the relationship between smoking and the development of clinical OA is weak (18).

The presence of airway hyper-responsiveness (AHR) (19,20) and rhinitis (20,21) before entering a workplace in which HMW agents are present is an independent risk factor for subsequent immunoglobulin E sensitization to these allergens. Furthermore, the development of occupational rhinitis during exposure often precedes the occurrence of OA (22,23). However, the predictive value of work-related nasal symptoms is only 11.4% for the subsequent development of probable OA in workers exposed to laboratory animals over a follow-up period of 30 to 42 months.

Genetic factors likely play a role in the development of OA. Certain human leukocyte antigen class II molecules were found to be either risk factors for or protective factors against OA due to various LMW and HMW agents (24). Genes associated with T helper cell 2 cell differentiation may also play a role in the development of OA. Genes involved in the protection against oxidative stress, such as those coding for glutathione-S-transferase and N-acetyltransferase, have been associated with an increased risk of isocyanate-induced OA or a protective effect. Overall, the currently available information indicates that genetic markers have a low predictive value in identifying susceptible workers. In addition, there is convincing evidence that a wide variety of environmental factors can interact with genetic determinants to affect disease susceptibility.

CLINICAL PRESENTATION SUGGESTIVE OF SENSITIZER-INDUCED ASTHMA

Sensitizer-induced OA should be suspected in every worker with new-onset asthma or in workers whose asthma has become difficult to control. Although OA has been described primarily in subjects who did not have asthma before their occupational exposure, approximately 20% of individuals with OA report having childhood asthma or asthma onset before entering the workforce (25,26). Therefore, OA should not be ruled out based only on the timing between the onset of asthma and the beginning of the occupational exposure.

Although the respiratory symptoms (eg, wheezing, dyspnea, chest tightness, cough and sputum production) are similar to those encountered in non-work-related asthma, their occurrence is usually modulated by the work exposure. The symptoms can start at the beginning of the work shift or toward its end, or even after working hours, with remission or improvement during weekends and holidays. Rhinitis is associated with respiratory symptoms in the majority of cases of OA and often precedes the occurrence of the respiratory symptoms, especially with HMW agents. Although a thorough clinical and occupational history must be carefully recorded, the diagnosis of OA cannot be made only on the basis of a compatible history, which has a low positive predictive value (27). A comprehensive investigation should be performed to accurately diagnose OA.

TABLE 2
Pooled estimates of sensitivity and specificity of skin prick testing, airway responsiveness and peak expiratory flow monitoring compared with specific inhalation challenge

Test	Sensitivity	Specificity
Skin-prick tests to occupational agent(s)		
High molecular weight	80.6 (69.8–88.1)	59.6 (41.7–75.3)
Low molecular weight	72.9 (59.7–83.0)	86.2 (77.4–91.9)
Airway hyper-responsiveness (single test)		
Low molecular weight	66.7 (58.4–74.0)	63.9 (56.1–71.0)
High molecular weight	79.3 (67.7–87.6)	51.3 (35.2–67.2)
Various agents	83.7 (66.8–92.9)	48.4 (25.9–71.6)
Airway hyper-responsiveness (serial tests)		
Low molecular weight	67.7 (42.6–85.3)	65.6 (41.1–84.0)
Various agents	50 (35.5–64.5)	66.8 (53.3–78.0)
Peak expiratory flow rate monitoring		
Low molecular weight	86.7 (59.5–96.6)	90 (53.3–98.6)
Various agents	63.6 (43.4–79.9)	77.2 (66.5–85.2)

Data presented as % (95% CI)

DIAGNOSTIC TESTS PERFORMED IN INDIVIDUALS WITH SUSPECTED SENSITIZER-INDUCED OA

Immunological assessment

Although immunological tests are limited by the lack of standardized, commercially available reagents for skin and in vitro tests for diagnosing OA, they bring useful information when available. The pooled sensitivity and specificity of skin-prick testing compared with specific inhalation challenges (SIC) is reported in Table 2 (28). Most in vitro tests used to assess specific sensitization to occupational chemicals remain research tools at present.

Respiratory function tests

In workers with a clinical and occupational history compatible with OA, the diagnosis of asthma needs to be confirmed by documenting reversible airflow limitation and/or AHR (29). However, the lack of AHR does not exclude the diagnosis of OA in individuals who have been removed from exposure. The work-relatedness of asthma should be assessed through serial measurements of peak expiratory flow (PEF) and/or AHR at work and off work, and/or SIC in the laboratory or at the workplace. The pooled estimates of sensitivity and specificity of the measure of AHR or PEF are reported in Table 2.

SIC tests

SIC tests consist of exposing indviduals to the suspected occupational agent in the laboratory and/or the workplace (30). These tests are considered to be the gold standard; however, they are time consuming and require specialized facilities available in only a few centres. SIC tests are especially useful when: the diagnosis of OA remains in doubt after serial monitoring of PEF or AHR; a patient clearly has OA, but the causal agent needs to be identified; a new agent is suspected of causing OA; and the patient cannot be returned to the hazardous workplace. A false-negative response may occur if the wrong agent is used or if the exposure conditions are not comparable with those in the workplace.

Noninvasive measures of airway inflammation

Sputum cell counts: An increase in sputum eosinophil counts has been shown to occur 7 h after exposure to occupational agents and persist 24 h after exposure (31). An increase in sputum eosinophil counts >3% after the first day of exposure during SIC appears to be one of the most accurate parameters for predicting the development of an asthmatic response on subsequent exposures, with a sensitivity of 67% and a specificity of 97% (32).

Exhaled nitric oxide: Previous studies have reported that an increase in fractional exhaled nitric oxide (FeNO) was not uniform among subjects who experienced a positive asthmatic reaction during SIC (33). The measurement of FeNO as a surrogate marker for eosinophilic airway inflammation is simple and feasible in almost all patients, and provides immediate results, but is more sensitive to confounding factors, such as smoking, atopy and treatment with inhaled corticosteroids, compared with sputum eosinophil counts (34). Additional evidence is needed before recommending the use of FeNO in the routine investigation of OA.

CONCLUSION

OA should be suspected in every worker with new-onset asthma or whose asthma becomes difficult to control. Although gathering a thorough clinical and occupational history is essential, a comprehensive investigation should be performed to demonstrate the relationship between the occurrence of asthma and the exposure to a specific agent at the workplace. Making an accurate diagnosis of OA is crucial because of the significant social and financial consequences associated with this diagnosis.

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