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Review

Occupational asthma and related respiratory diseases

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SUMMARY

Epidemiological evidences and clinical as well as experimental observations have suggested a link between asthma and occupations. This relationship also involves other aspects like non-immunologic exposures in the environment that can increase the chance of developing work related asthma and respiratory diseases. The purpose of this pamphlet is to supply information of work related diseases, which will give patients suffering with asthma, an intelligent understanding of their disease, and thus stimulate their interest so that they will cooperate more readily with their allergist. Recognizing the symptoms, causes, risk factors, diagnosis and treatment is an important part of managing occupational asthma and related diseases, so that it helps in decline of this rapidly increasing prevalence throughout the world.

Key words: Occupational asthma; Allergist

INTRODUCTION

Asthma is a problem worldwide, and the diseases social burden and costs to health care systems are substantial (National Heart LaBI, 2002). The clinical evaluation of newly developed asthma in an adult should always include consideration of his occupational environment, since an abundance of different exposures, which are known causes of asthma, occur in workplaces (Torben Sigsgaard *et al.*, 2004). Work related asthma accounts for at least 10% of all cases of adult asthma (Sami youakim, 2001). Out of which 90% of cases being attributed to an allergic response. According to population based cohort study including the entire employed Finnish population aged 25 - 59 years, the fraction of work related asthma was 29% for males and 17% for females (Karjalainen *et al.*, 2000).

Asthma has emerged as the principle occupational lung disease. The incidence of diseases caused by mineral dust has declined recently in postindustrial countries. Each year, new substances are introduced into workplace, and some are found to cause lung disease (Kern *et al.*, 1998). More than 250 substances found in the workplaces cause occupational asthma (Brooks *et al.*, 1998). The airways, from nares to alveoli, come into contact with 14,000 liters of air in the workplace during a 40 h workweek. Physical activity can increase ventilation, and thus exposure to contaminants, up to 12 times the levels at rest. As ventilation increases breathing shifts from nasal to a combination of oral and nasal, allowing a greater volume of air to bypass the cleansing nasopharynx and further increasing the exposure of the lower airways to inhaled materials. Strong irritants like ammonia produce an aversive

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response, whereas materials with little sensory effectors such as asbestos can be inhaled for prolonged periods and result in serous injury (William, 2005).

ASTHMA

Asthma is a disease in which the airways (breathing passages) tend to narrow too easily and too much in response to a wide range of triggers. Asthma symptoms include wheezing, chest tightness, difficulty in breathing, shortness of breath, and sometimes cough. Asthma is a treatable health condition. Although at present there is no cure, with good management most people with asthma can lead normal, active lives. It is important to be assessed and cared for by a doctor with a good knowledge of current asthma management.

WORK RELATED ASTHMA

It is defined as prexisting or concurrent asthma that is exacerbated by workplace. Workplace exposure to certain chemicals or dusts can induce asthma. Work related asthma is induced or incited by substances or conditions specific to the work place. It has become the most common occupational respiratory disease in many countries. Approximately 10% of all cases of adult asthma are attributed to an occupational etiology. Quick recognition and control of workplace exposures are important. Work related asthma categorized into two distinct subsets

WORK AGGRAVATED ASTHMA

Work aggravated asthma is caused by mechanical irritation of the airways from nonallergic dust and by chemical irritation. Persons with work aggravated asthma have a history of preexising asthma.They have recurrent asthmatic episodes that are triggered by a nonspecific mechanisms such as cold temperature, excessive exertion, or exposue to irritant aerosols including dusts, fumes, vapors and gases.

OCCUPATIONAL ASTHMA

Occupational asthma develop as a direct result of workplace exposure.Two forms of occupational asthma are recognized.

a. Reactive airway dysfunction syndrome (RADS) (also known as irritant-induced asthma or Nonimmunological occupational asthma)

RADS usually develop after a single, very high exposure to an irritant chemical (Bernstein *et al.*, 1999). These causal agents include ammonia, chorine gas, and hydrochloric acid. These exposures are usually the result of accidents, spills, or equipment failure. Workers who survive massive exposures usually manifest asthma symptoms within 24 h. Whether recurrent exposure to lower levels of respiratory irritants leads to irritant induced asthma is currently the matter of debate (Tarlo, 2000).

b. Latency-associated occupational asthma (also known as Allergic occupational asthma (AO) or Immunological occupational asthma)

Allergic occupational asthma is subdivided into two groups based on the molecular weight of the etiologic agent: high-molecular weight (HMW) substances (Beach *et al.*, 1998) and low-molecular weight (LMW) substances, which are commonly defined as having a molecular weight less than 1 kilo Dalton (Maestrelli *et al.*, 1998) This division is made because the mechanism of disease is better understood for the HMW substances than for the LMW substances. It is generally accepted that agents of both substance types cause occupational asthma by an immune mechanism. The mechanism for allergic occupational asthma caused by HMW substances is a type I, IgE-mediated process. The mechanism caused by LMW substances is less well defined. IgE and IgG antibodies, as well as cell mediated hypersensitivity, may be involved (Mapp *et al.*, 1999). Allergic occupational asthma has been attributed to several hundred substances found in the workplace, and more are being

identified HMW substances typically produce early reactions.

Symptoms begin 10 to 20 min following exposure and may gradually resolve with or without treatment over the next one to two h. LMW substances commonly produce delayed reactions that are associated with significant airway inflammation. Symptoms begin three to four h after exposure and peak after eight h. If the delayed reaction occurs after the worker has left the workplace, the relation to work exposure may not be made. Dual reactions (an early reaction followed by a late one) and atypical reactions have also been described. Reaction patterns cannot be used to identify suspected causal agents because they are not specific to the molecular-weight size grouping. Early, late, dual, and atypical reactions can occur with LMW and HMW substances (Perrin *et al.*, 1991).

OCCUPATIONAL RESPIRATORY DISEASES

Chronic obstructive pulmonary disease (COPD) or chronic airflow limitation

Chronic obstructive pulmonary disease is defined as a syndrome characterized by abnormal tests of expiratory flow that do not change markedly over periods of several months of observation. COPD is the sixth cause of death in the world and affects 4 - 6% of people more than 45 year of age. The relationship of smoking and COPD has been also observed in many studies conducted the world over. Cigarette smoking remains the predominant cause of chronic obstructive pulmonary disease, but many occupational dusts can cause or contribute to chronic airflow limitation or emphysema (Hendrik, 1996; Sunyer *et al.*, 1998). Chronic exposure to fumes, chemical substances, and dust in the workplace represents one of the main factors for development of COPD and asthma. Grain dust, coal, and other mineral dusts; isocynates; heavy metal adhesives; and welding fumes are a few relevant causes of COPD and asthma among workers in mining, quarrying, construction, agriculture, textile manufacture, wood and paper industries. Cadmium causes emphysema after prolonged exposure at levels lower than those for other mineral dusts (Davison *et al.*, 1988). Cotton dust, a complex mixture that contains bacterial endotoxin, can cause chronic bronchitis (Beckett *et al.*, 1994), occupational asthma (Bouhuys *et al.*, 1967), inhalation fever, and chronic airflow limitation (Christiani *et al.*, 1994). While chronic airflow limitation is caused by silica or beryllium dust, (Adrews *et al.*, 1969).

ALLERGIC RHINITIS

Allergic rhinitis is the most common allergic condition worldwide, affecting over 150 million people in North America, Europe and Japan alone, and prevalence is increasing. Allergic reactions in the nose are mediated by similar antigen-antibody responses that interact with specific IgE molecules bound to nasal mast cells and basophils. The initial nasal mucosal response is vascular dilation, increased permeability, rhinorrhea and congestion (Naclerio *et al.*, 1997 and Woodin *et al.*, 1998). In patients with allergic rhinitis, mast cells and basophils increase both in number and in reactivity. Thus, when airborne allergens enter the nose, they push the lymphocytes into action to produce antigen-specific IgE, and when the person is reexposed to the allergen, the IgE bound to the mast cells triggers a release of inflammatory mediators. These mediators include histamine to cause the pruritus and vascular permeability, leukotrienes to contract the smooth muscle and cause mucus secretion, and thromboxanes to cause the smooth muscle to spasm. Numerous substances in the workplace, from latex-coated cornstarch particles to common cleansing solutions, cause allergic and irritant upper respiratory airway disease. The presence of several risk factors, both occupational and nonoccupational rhinitis can contribute to the

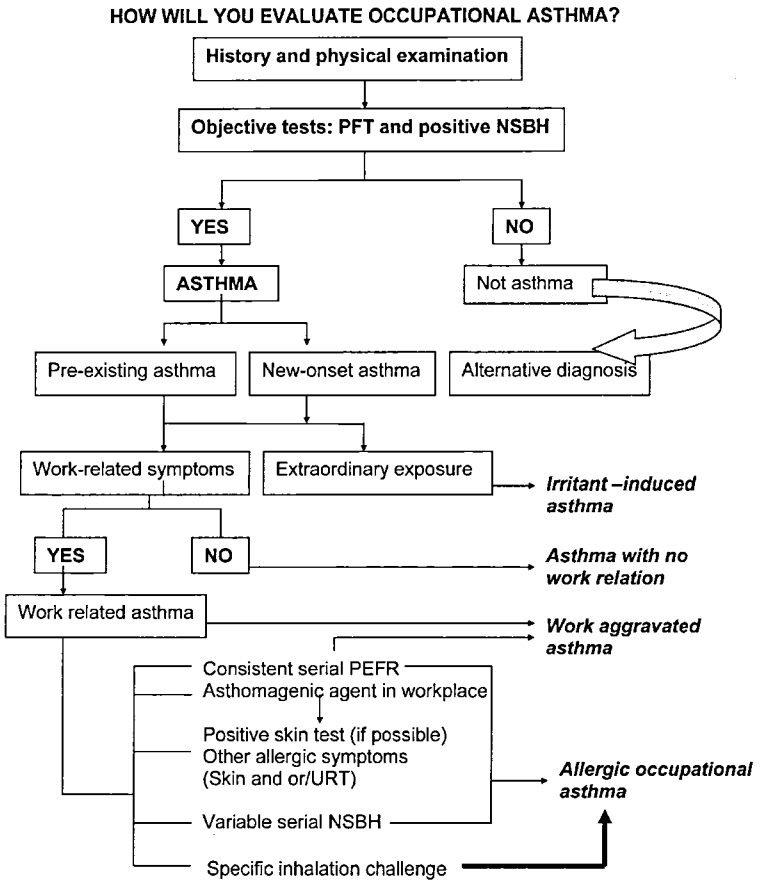

Fig. 1. An algorithmic approach to the evaluation of work-related asthma. PFT, pulmonary function test; NSBH, nonspecific bronchial hyper-responsiveness; RADS, reactive airway dysfunction syndrome; PEFR, peak expiratory flow rate; URT, upper respiratory tract (Chan-Yeung, 1995; Tarlo *et al.*, 1998; Friedman-Jimenez *et al.*, 2000).

Table 1. Causative agents of reactive airway dysfunction syndrome (RADS)

Causative agents	
2-Diethylaminoethanolamine	Phosphoric acid
Acetic acid	Silicon
Anhydrous ammonia	Silo gas
Bleaching agents	Smoke (inhaled)
Burned-paint fumes	Sodium hydroxide
Chlorine gas	Sulfuric acid
Constituents of free-base cocaine	Tear gas
Floor sealant	Toluene diisocyanate
Hydrochloric acid	Trichlorosilane
Hydrogen sulfide	Welding fumes
Locomotive/diesel exhaust	Zinc chloride
Phosgene	

Adapted with permission from Brooks S. Occupational and environmental asthma In: Rom WN ed. Environmental and Occupational medicine 3rd ed. Philadelphia Lippincott-Raven, 1998.

Table 2. Examples of occupations and associated agents known to cause immunological occupational asthma

Occupations	Agents	Respiratory disease
Exposure to high-molecular-weight substances Bakers, farmers, flour mill workers, grain elevator workers, food workers	Flour, grain dust, soybean	Asthma, Rhinitis, Laryngitis
Silk-processing workers, research laboratory workers, insect-raising facility workers	Insects	Rhinorrhea
Prawn, snow-crab, and fish processors	Seafood, other marine organisms	Rhinorrhea
Laboratory workers, animal handlers, veterinarians, Zoo keepers	Animal dander or urine, fungi, endotoxin,	Hypersensitivity, Pneumonitis
Detergent producers, food industry workers, blood-processing laboratory workers	Enzymes e.g. bacillus subtilitis	Inhalation fever
Carpet manufacturing workers, latex-glove manufacturing workers, health care workers	Gums, latex	Asthma with latency
Sween breeding	Swine dander	
Exposure to low-molecular-weight substances Plastic, rubber or foam manufacturing workers, spray painters, foam insulation installers	Diisocyanate (toluene, diphenylmethane, aliphatic amines hexamethylene)	Asthma with latency
Soldiers, electronic industry workers	Colophony	Bronchitis
Woodworkers, carpenters foresters, artisans	Plicatic acid (Western red cedar wood dust) like pine, iroko, oak	Pulmonary fibrosis
Refinery workers	Metals (chromium, platinum, nickel)	Lung cancer
Textile workers, cotton workers	Dyes	COPD
Plastic and epoxy resin workers	Anhydrides	Asthma with latency
Adhesive handlers	Acrylates	
Pharmaceutical industry workers	Pharmaceuticals	
Health care workers, ebalmers	Glutaraldehyde, latex, formaldehyde	Bronchitis

Information from (Banks *et al.*, 1998; Parker *et al.*, 1998; Beach *et al.*, 1999).

development of disease. Symptomatology of allergic rhinitis includes rhinorrhea; conjunctivitis; sneezing; nasal congestion; and itchy eyes, nose, ears, or palate. Chromic acid and other substances produce nasal ulceration and perforation of the septum, where as nickel and certain wood dusts cause nasal carcinoma (Imbus *et al.*, 1987 and Litovitz *et al.*, 1990).

ASBESTOSIS AND ASBESTOS-RELATED DISEASES

Asbestosis is one of the pneumoconioses, a group of diseases caused by accumulation of mineral dusts in the lung tissue. Asbestosis usually develops after 5 - 10 years of exposure to high levels of asbestos. It can progress even after stopping exposure. The fibers cause scarring of the lungs. The person affected may feel breathless after walking a short distance. Eventually the lungs may fail and death may follow. The fiber may, diffuse interstitial fibrosis of the lung that results from complex inflammatory and immune responses to inhaled asbestos fibers. Fiber size, intensity and duration of exposure, smoking history (including passive smoking), and individual susceptibility all play a role in the development of asbestosis. There is a dose-response relationship such that workers with higher exposures to asbestos are more likely to develop asbestosis. Environmental asbestos exposure alone rarely causes pulmonary fibrosis. However, Magnani *et al.* (1998) did report a case of environmental asbestos exposure resulting in asbestosis.

LUNG CANCER

Asbestos causes cancer of the lung similar to that caused by smoking. A person who smokes and is exposed to asbestos is at a higher risk of lung cancer than one who does not smoke. How asbestos fibers cause lung cancer continues to be studied extensively. However, it is known that asbestosis is not necessary for the development of asbestos related lung cancer (Magnani *et al.*, 1999). Montizaan *et al.* (1989) and Egilman *et al.*(1996) reported that asbestos-related lung cancer was probably caused by the interaction of the asbestos fiber and nuclear material in the cell resulting in mutation. Nelson *et al.* (1998) more recently reported that the prevalence of k-*ras* codon 12 mutations seen in lung adenocarcinoma tumors was higher in those with occupational asbestos exposure, with the intensity of exposure to asbestos and the time since initial exposure being the most factors. At least 12 substances found in the workplace are classified as human lung carcinogens. There is a wide range of other malignancies related to asbestos exposure. These include pleural and peritoneal mesothelioma, laryngeal cancer, and gastrointestinal cancers such as esophageal, stomach, colon, and rectum. Asbestos fibers may also travel to the peritoneum via the lymphatic system. Mesothelioma is almost exclusively due to asbestos exposure, even if the exposure was of short duration (Claudia *et al.*, 2000).

Occupational exposure is estimated to account for approximately 5% of lung cancers in the United States (Doll *et al.*, 1981) The majority of these cancers are caused by asbestos, followed by radon, silica, chromium, cadmium, nickel, arsenic, and beryllium (Steenland *et al.*, 1996). Cigarette smoke and asbestos interacts strongly in causing bronchogenic carcinomas, and the risk of carcinoma is greater in persons with the interstitial fibrosis of asbestosis (Weiss, 1984). There is a wide range of other malignancies related to asbestos exposure.

BRONCHITIS AND BRONCHIOLITIS

Soluble gases are absorbed by the upper-airway mucosa, whereas less soluble gases penetrate to the alveoli. The location of particle deposition in the airways is determined by the concentration and size of the particles. Particles that are 10 μm or more in diameter are deposited in the nose and pharynx, whereas particles that are 5 μm in diameter or smaller may penetrate to the alveoli. Particles of intermediate size are deposited in differing proportions at intervening levels. Acute bronchitis results from mucosal inflammation after exposure. The condition is treated with inhaled corticosteroids until it subsides. Chronic irritation can lead to hyperplasia and hypersecretion of the mucous glands. A cough with mucus production on most days for three months per year over two consecutive years is diagnostic of chronic bronchitis and correlates with histologically confirmed mucous hyperplasia (De Haller *et al.*, 1995). Many occupational substances produce industrial bronchitis, just as cigarette smoke causes smoker's bronchitis (Morgan, 1978). Bronchitis is found in persons whose occupation involves exposure to dust or who work in chemical and food processing, mining, storage and processing of grains and feeds, cotton-textile milling, and welding (Korn *et al.*, 1987; Fishwick *et al.*, 1997).

Bronchiolitis obliterans, the narrowing and filling of bronchioles was first described in soldiers who had been exposed to chlorine and phosgene gases, and it was later described in survivors of accidental workplace gassings with chlorine and in workers exposed to nitrogen dioxide generated by freshly stored hay (silo filler's disease). It is manifested by dyspnea, chest tightness, and irreversible airflow obstruction, with onset several hours to days after a heavy exposure to irritant gas (Wright, 1993).

INTERSTITIAL LUNG DISEASE

Most inhaled dust is filtered out by the upper

airways or cleared by the ciliated epithelium of large airways. If these defenses are overwhelmed by fine dust (less than 10 μm in diameter), however, the lung reacts with an alveolar and interstitial inflammation that may culminate in disease. Pulmonary fibrosis, alveolar proteinosis, lipoid pneumonia, hypersensitivity pneumonia granulomatous disease, inhalation fever are the common interstitial lung diseases.

FIBROTIC DISEASE

In the 25 years from 1968 through 1992, a total of 100,890 death certificates in the United States listed pneumoconiosis (dust-associated disease of the lungs) as a contributing or primary cause of death. The majority of these cases were coal worker's pneumoconiosis, silicosis, and asbestosis (Work related disease surveillance report, 1996). The rate of death from pneumoconiosis is declining, but silicosis remains prevalent in many regions and industries and has recently been recognized as a disease of construction workers who perform surface-rock drilling and cutting. Dusts such as coal, cobalt, talc, and kaolin (Morgan *et al.*, 1988) which are encountered less frequently in industry than silica, are important causes of new cases of disease. Diffuse alveolar-filling disease (presenting as dyspnea with interstitial abnormalities on the chest x-ray film) due to the overproduction of surfactant by type II alveolar pneumocytes may be caused by intense exposure to fine silica dust, and it has been reported after several other types of occupational exposure to dust. Lipoid, alveolar-filling pneumonia can be caused by the inhalation of fine oil mist (Cullen *et al.*, 1981).

GRANULOMATOUS DISEASE

Hypersensitivity pneumonitis, an acute febrile pneumonitis with peripheral leukocytosis, is caused by immunologic reaction to a variety of inhaled substances. It may have acute, subacute, and chronic forms, depending on the degree of exposure, the duration of exposure, and the susceptibility of the patient. A growing list of workplace substances have been identified as capable of causing this response (Reynolds, 1991). Cigarette smoking and intense exposure predispose workers to sensitization to some substance (Barker *et al.*, 1998). An acute episode often has its onset late in the day or in the evening after exposure in the workplace.

INHALATION FEVER

Inhalation fever is characterized by self-limiting fever after a single exposure, with peripheral leukocytosis but minimal or no lung inflammation. Cytokines from resident lung cells cause demargination of pulmonary vascular leukocytes, and prostanoids that are produced by these cells act at the hypothalamus to produce the febrile episode, which usually begins up to 6 h after exposure and lasts less than 12 h (Blanc *et al.*, 1991). The typical history of exposure involves indoor work in the winter in which an organism-contaminated water-spray system is used to humidify air (Pickering *et al.*, 1982) disturbing an accumulation of moldy hay, grass, compost, mulch, or wood chips; or heating zinc to the point of vaporization (e.g., in welding galvanized steel). Inhaled combustion products of polytetrafluoroethylene (Teflon) may cause fever and hemorrhagic pneumonitis (Brubaker, 1977).

CONCLUSION

Although there are some unsolved issues in the diagnosis of OA, most physicians rely on a combination of patient history including occupation, knowledge of the causative agents in working environment, medical history, clinical examination, serial measurements of lung function, immunological tests, specific and/or unspecific bronchial challenge tests and imaging studies are all essential to the

diagnosis of occupational asthma and related respiratory disorders. India urgently requires modern Occupation Health Safety (OHS) legislations with adequate enforcement machinery and establishment of centers of excellence in occupational medicine, to catch up with the rest of world.

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