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Diagnosis of Occupational Asthma: Review

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Work related asthma is a common problem and well documented in the literature. It results from exposure to an irritant or sensitiser agent at the workplace. The mechanism of occupational asthma is a complex process. The diagnosis of occupational asthma can be difficult but the combination of both occupational history and objective assessment of asthma is very helpful. Physicians should be aware of this serious and preventable medical condition.

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Definition

Occupational asthma (OA) can be defined as "variable airways narrowing causally related to exposure in the working environment to airborne dust, gases and fumes"[1,2]. About 250 agents can cause occupational asthma[3] . Different conditions can be listed under the term Asthma in the workplace, including OA, work aggravated asthma and variants such as byssinosis, grain dust induced respiratory disease and aluminum potroom asthma. Two types of OA have been recognized: (1) OA with latency period is most common and develop after a period of exposure for few weeks, to several years[4]. It is caused by exposure to high molecular weight agents (MW > 5000 daltons) eg. cereals and enzymes.. etc. or exposure to low molecular weight agents (MW < 5000 daltons) eg. acid anhydrides and platinum salts ... etc. (2) OA without latency period which includes reactive airways dysfunction syndrome (RADS) and here it follows exposure to high concentration of irritant gases, fumes or chemicals on one or several occasions[5].

Mechanism

Agents at the workplace cause occupational asthma through immunologic and non immunologic mechanisms. Most of the high molecular weight compounds induce asthma by producing specific IgE and sometimes specific IgG antibodies. Some of the low molecular weight compounds such as acid anhydrides and platinum salts act as haptens and induce specific IgE antibodies by combining with a body protein[6,7].

In either case it leads to cascade of events causing the activation of inflammatory cells. For other types of low molecular weight agents such as isocyanates the mechanism of OA is not well known, however the role of T-lymphocytes has been suggested[8]. Isocyanates in vitro in

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high concentration are found to act as beta2 adrenergic blocking agent[9] and plicatic acid is able to activate complement[10]. Also neurogenic mechanisms with secretion of neuropeptide which induce asthma has been reported[11].

The mechanism of asthma in RADS is unknown, however in some studies fibrosis of the bronchial wall and fewer T lymphocyte were found suggesting the absence of an immunologic mechanism[12,13].

Clinical presentation

The typical symptoms of asthma such as coughing , wheezing and chest tightness may occur in relation to work after exposure to the causative agent. These symptoms may be worst at night and become worst as the week continue. At the onset of asthma most workers have improvement over the weekends and vacation. At a later stage, recovery may takes several days or weeks after exposure ceases.

A high proportion of patients with OA also have allergic or conjunctivitis especially in workers exposed to high molecular weight agents[14].

Outcome

The majority (60% to 80%) of patients with OA do not recover several years after removal from exposure. The severity of asthma in these patients varied from mild to severe chronic asthma and they have persistent bronchial hyper-responsiveness. A good prognosis was associated with shorter duration of symptoms. So early removal from further exposure increase the likelihood of recovery. Continuous exposure is associated with a worsening asthma[15,16].

Diagnosis of occupational asthma

It is first important to establish the diagnosis of asthma then to establish that asthma is due to exposure at the workplace. Diseases that mimic asthma include hypersensitivity pneumonitis, sarcoidosis, bronchiolitis, congestive heart failure, and vocal cord dysfunction. One needs to think about them when the patient is referred for evaluation of OA. There are different steps involved in the investigation of asthma which include: history, immunological tests, lung function tests, peak expiratory flows and bronchial challenge tests and exposure assessment.

History

The occupational history is the key tool in the assessment of patients with possible work related asthma. The classical history of OA is that a worker's symptoms are worse at work, improving over the weekend or holidays. However, this pattern is not present all the time. In many cases the symptoms are worse at night and toward the end of the week when OA is triggered by agents that cause a late phase reaction. Also asthma may react to non specific irritants outside the workplace such as cold air, fumes or exercise. The occupational history should include unusual events at the time of onset of symptoms such as new job assignment, use of new chemical and accidental exposure to irritants. Personal risk factors such as atopy (in case of high molecular weight agents), smoking and ? non specific bronchial hyper-responsiveness are helpful in the history to investigate for OA. A previous history of asthma may postpone the diagnosis of OA[17]. The disease should be suspected in any person exposed at work to agents

known to cause OA. So physicians who practice in areas where isocyanate exposure is prevalent should have a higher index of suspicion for OA. The occurrence of rhinoconjunctivitis at work is suggestive of OA[18].

The assessment should include a detailed history of the worker's symptoms, past and present jobs, specific job duties and work process and similar symptoms in his coworkers. A history suggestive of OA is not sufficient to make the diagnosis of OA, so the diagnosis should be confirmed by objective tests. The questionnaires to diagnose OA are a sensitive but not specific tool. Furthermore, it was found that the positive predictive value of the questionnaire was only 63% while its negative predictive value was 83%, therefore it is not a satisfactory means of diagnosing OA[19].

Immunological testing

Allergy skin tests with the appropriate extract of the suspected agents and with a control agent and the presence of IgE or IgG are helpful to diagnose OA due to high molecular weight compounds. However a negative immunologic test to these allergens cannot entirely exclude OA but make it unilikely[20]. Unfortunately there are no standardized occupational allergens commercially available at the present[21]. Furthermore close attention should be paid to the laboratory's data concerning the reliability, reproducibility, and validity of their methods to investigate for IgE and IgG[22]. Furthermore, medications such as antihistamine can affect the result of skin prick tests.

Skin tests cannot be used for small molecular weight agents. Furthermore the finding of IgE or IgG in the worker's sera with exception of acid anhydrides and platinum salts cannot be used to diagnose OA due to low molecular weight compounds[23].

Pulmonary function tests

The diagnosis of OA should be confirmed by the demonstration of airflow limitation with improvement after bronchodilator treatment. Most workers investigated for OA have normal spriometry. Pre-shift and post-shift measurements of FEV1 has not proved to be a sensitive or specific tool for the investigation of OA and it is impractical[24,25].

Peak expiratory flows

Serial measurements of peak expiratory flow rate (PEFR) has been used in the assessment of OA. The sensitivity and specificity of PEFR was found to be 81% to 89% and 74% to 89% respectively when compared to the gold standard (specific challenge tests)[26]. A minimum of four measurement per day of PEFR has been advised[27].

PEFR may underestimate or overestimate changes in airway caliber as assessed by FEV1. Furthermore it is effort dependent requires collaboration of the worker which is not always obtained[28,29]. Combining PEFR and nonspecific bronchial reactivity did not add much to the sensitivity of PEFR, but if both showed changes the diagnosis of OA is highly probable[30].

For optimal use of PEFR in assessing OA, at least monitor for a minimum of 2 weeks both at work and away from work, educate patient on how to use it, instruct patient to use beta agonists

as needed, continue using inhaled steroids and other medication in stable manner, and keep diary of information about work hours, unusual tasks and other conditions at work and off work[31].

Nonspecific bronchial challenge test

Different agents used to demonstrate bronchial reactivity, including histamine, methacholine, cold air, fog, exercise and others. Of these histamine, methacholine are the most widely used and best standardized. Different protocols are available on how to use histamine and methacholine. A PC_{20} of 8 mg/ml or less that reflects bronchial reactivity (some people consider a PC_{20} of 4-8 mg/ml is an equivocal result) was found to differentiate patients with asthma from normal healthy subjects[32].

There are several factors that influence the response to methacholine or histamine challenge tests. These include: upper respiratory tract infection, prior exposure to allergens and the use of medication. H_1 inhibitors block the effect of histamine (should be withheld for 48 hours) whereas the anticholinergic drugs block the effect of methacholine. All bronchodilators inhibit the effect of histamine and methacholine , so should be withheld for appropriate length of time (from 6 to 24 hours depending on the half life of the medication) before the challenge test. Disodium cromoglycate and steroid do not effect the response of histamine or methacholine challenge test.

The output of the nebulizer and the particle size of the aerosol generated and the breathing pattern of the subject also affect the response to the challenge test.

Bronchial responsiveness is present in other conditions such as rhinitis and chronic obstructive lung disease. On the other hand, the absence of bronchial reactivity in a worker assessed shortly (minutes to hours) after symptoms virtually excludes asthma. Bronchial reactivity may be normal in worker who has left the work for several days. Therefore, airway hyper-responsiveness can be performed on a workday and then reassessed after at least 2 weeks away from work to confirm the diagnosis of OA[33].

Specific challenge test

This method is considered the gold standard for the diagnosis of OA, although in practice it is rarely needed because it carries certain risks. Testing should be performed only in specialized centers where the experience in administration of the powder, aerosol and gases and in the monitoring of the dose and resuscitation of the patient are available.

There are three indications for specific challenge tests:

1. To document a previously unrecognized agent in the workplace that cause OA.

2. To establish the diagnosis of OA when other means (history, PEFR,.etc.) are equivocal.

3. To confirm the diagnosis of OA to specific agent when the worker is exposed to multiple agents at the workplace[34].

The test conducted inside chamber and the subject's work is simulated as closely as possible. Then inhalation is discontinued when a 20% fall in FEV1 occurs.

In case of high molecular weight agents the initial dose of the allergen for inhalation should be the one that produce a wheal on skin test of less than 3mm then gradually increased. On the other hand for low molecular weight agents and because skin tests with these agents are not possible, the initial dose should be guided by history and the degree of non specific bronchial reactivity.

Lung function test should be performed before, during and after challenge for at least 8 hours and the patient should be instructed to monitor their PEFR every 2 hours in the evening until bedtime. This is important to look for immediate, late and dual asthmatic reaction. Furthermore, spirometry should be monitored in a control day.

Drugs such as beta agonists should be withheld before the test for the appropriate length of time. For inhaled steroids and sodium cromoglycate, they should be continued but taken in the evening of each challenge test at the same total dose to avoid exacerbation of asthma when these medications withheld.

A workplace challenge test could be performed through serial measurements of the lung function test before and during the working shift.

A negative workplace or laboratory challenge test does not exclude the diagnosis of OA in a worker who left work for long time and became desensitized. False negative tests may be due to exposure to the wrong agent in the challenge test or the method of testing is not correct[35].

Exposure assessment

Occupational medicine physician should conduct a walk through of the workplace, review the industrial hygiene data, and the Material Safety Data Sheets (MSDS) in order to look for a known sensitizer at the workplace. Discussing the work condition with employer and union may be helpful in the assessment of OA after obtaining the consent of the patient so as not to jeopardize patient confidentiality. Temporary work restrictions may help to confirm the relationship of workplace to asthma.

To sum up, the diagnosis of OA can be difficult but the combination of history and objective assessment of asthma is very helpful. The following table illustrate the advantage and disadvantage of various methods used in the diagnosis of OA.

Table. **Advantage and disadvantage of diagnostic methods for OA (Adopted from reference 4)**

Method	*Advantage*	*Disadvantage*
Questionnair	simple, sensitive	low specificity
Immunologic testing	simple, sensitive	only for high molecular weight and some low molecular weight agents identify sensitization, not disease, majority of allergen not available commercially
Bronchial reactivity to histamine and methacholine	simple, sensitive	not specific for asthma or OA, OA not ruled out by negative test.
Pre and post shift work FEV1 measurement	simple, inexpensive	low sensitivity and specificity
PEFR	relatively simple and inexpensive	require patient's cooperation and honesty, not as sensitive as FEV1 in assessing airway caliber, no standardized method of interpreting the graph
Specific inhalation challenge in hospital laboratory	if positive confirmatory	diagnosis is not ruled out by negative test (eg. if wrong agent or subject no longer at work), expensive, few referral centres.
Serial FEV1 measurements at work under supervision	if negative rules out diagnosis when patient tested under usual work conditions	a positive test may be due to irritation, require collaboration of employer

Finally, there is a published algorithm in clinical investigation of OA[17]. So when there is a history of exposure to high molecular weight agent, positive skin test or finding a specific IgE or IgG is suggestive of OA if pulmonary function test confirm asthma. When these tests are not available a methacholine challenge test should be conducted. A negative methacholine test at the end of working shift for at least 2 weeks at work excludes the diagnosis of OA. A positive methacholine test, requires specific challenge test if available. In case of negative specific challenge test, this require PEFR monitoring to exclude OA.

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