Clinical Presentations and Investigations in Asthma

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Introduction

The term “asthma” emerged from an ancient Greek word which means to exhale with open mouth or to pant.1 An estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease.2 The prevalence of asthma has increased in the past few years. Asthma is characterised by phases of normalcy punctuated by attacks of breathlessness, wheeze and cough. It can present at any age and can have different clinical presentations. The only characteristics that are certain about asthma are its variability and its unpredictability. The increasing prevalence of the disease and its heterogeneous nature makes it important for us to diagnose the disease and its subtype correctly.

Clinical Presentation

What are the characteristics of asthmatic symptoms?

Asthma is characterised by breathlessness, cough, wheeze and chest tightness especially at night or in early morning 3 (Fig 1). The severity of these symptoms is variable. Symptoms occur in episodes. These may occur abruptly or may develop over a period of days or weeks. Some patients complain of asthmatic attacks mainly at night or in early morning. These episodes typically occur between 4 am and 6 am in the morning and they tend to wake up the patient.

The most common symptom of these patients is breathlessness that may be due to dynamic lung hyperinflation leading to difficult inspiration. Wheezing is usually polyphonic in nature due to its origin from many airways of different calibre. The cough is usually dry but sometimes may be associated with small amounts of sticky sputum. Sputum, when present, is white or green in colour indicative of peroxidase released by eosinophils and neutrophils.

What is the association of atopy with asthma?

A positive family history of atopy may be found in asthmatic subjects. The term atopy is the tendency of an individual to be hyper-responsive to certain allergens. It may be hereditary and occurs after an initial exposure with a particular allergen. It may present in various ways like eczema, allergic rhinitis, allergic conjunctivitis or allergic asthma.

What are the trigger factors of asthma?

Patients usually complain of exposure to some triggering or aggravating factors prior to the development of asthmatic attack. Such factors may be allergic and non allergic (Table 1). The common allergic trigger factors that may play a role in an asthmatic attack are house dust mite, pollen, fungal spore and pet. Cats are the most common household pets triggering asthma. Non allergic

Asthma

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Fig. 1: Characteristics of asthmatic symptoms
triggering factors include exercise, food, drinks, drugs, viral infections, air pollution, smoking, psychological factors and climatic variations.

Trigger agents can work singly or in combination and every effort should be made to identify these triggers and minimise their exposure. The attacks of asthma also vary greatly in severity. They may present as mild cough or as severe attacks of breathlessness.

What are common presentations of asthma in childhood?

Asthma may present in various ways and several of its phenotypes have been described over the years. A child may present to us in the following ways-

1. **Transient infant wheezing:** A young wheezing child may visit in the outpatient department. There may be no family history. Subsequently after the age of 3 years, the wheezing disappears. Such a clinical condition is termed as transient infant wheezing. Its prognosis is good.

2. **Non atopic wheezing of toddler:** In another type of presentation, a child may come with complains of wheeze and breathlessness. Wheeze does not disappear even after 3 years age. These children are non atopic but on persistent questioning, their parents may give history of lower respiratory tract viral infection. A child with respiratory syncytial virus infection may present in such a manner. These children respond well to leukotriene receptor antagonists. This type of wheezing is called as non atopic wheezing of toddler.

3. **Late onset childhood asthma:** In some cases asthma may develop around the puberty age. This is seen mainly in girls. It is associated with atopy, bronchial hyper-responsiveness and has low remission rate. This is called late onset childhood asthma.

4. **There is another set of children who continue to wheeze into adulthood. Risk factors for such kind of asthma include early age of onset, female gender, history of atopy, eczema, impaired lung functions and bronchial hyper-responsiveness.**

Table 1: Trigger factors of asthma

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<tr>
<th>Allergic trigger factors</th>
<th>Non-allergic trigger factors</th>
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<tr>
<td>House dust mite</td>
<td>Exercise</td>
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<td>Pollen</td>
<td>Food</td>
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<td>Fungal spore</td>
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<td>Pet</td>
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<td>Viral infections</td>
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<td>Gastro-oesophageal reflux</td>
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<td>Occupational factors</td>
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How does an adult asthmatic patient present?

Adult onset asthma can present in various ways as follows-

1. **Adult onset asthma or intrinsic asthma or non-atopic asthma:** Sometimes asthma starts after 40 years of age. Such patients are completely asymptomatic initially and then start having asthmatic symptoms. Such type of asthma is associated with higher degree of severity and is termed as adult onset asthma or intrinsic asthma or non-atopic asthma. This is characterised by female predominance and has more frequent association with nasal polyposis. The risk factors associated with this subtype are smoking and chronic rhinosinusitis. Atopy and a family history of asthma are often lacking.

2. **Asthma occurring after lower respiratory infection:** A subset of adult onset asthmatic patients have onset of asthma following a severe respiratory infection. The two organisms commonly causing respiratory infection in such cases are chlamydia pneumoniae and mycoplasma pneumonia.

3. **Aspirin exacerbated respiratory disease (AERD):** Another group of patients may be allergic to aspirin. This is called as aspirin exacerbated respiratory disease. It consists of symptom triad named Sampter’s triad which include asthma, chronic rhinosinusitis with nasal polyposis and reaction to aspirin. Symptoms usually manifest 30 minutes to 3 hours after ingestion of aspirin. It is a type of pseudoallergy which is non IgE mediated and manifests as bronchospasm and nasal congestion.

4. **Occupational asthma:** In some patients, asthma is triggered at workplace. This is termed as occupational asthma. Two kinds of triggers are seen at workplace. These are immunologic and non immunologic stimuli. In immunologic type, a time gap is usually present between exposure and onset of symptoms while in non-immunologic type, no such interval exists. Non immunologic stimuli comprise of various irritant gases, smoke, fumes and aerosols. Exposure to these agents produce a syndrome called as reactive airway dysfunction syndrome (RADS).

Immunologic stimuli are further divided into high-molecular-weight (e.g., flour, laboratory animal proteins) and low-molecular-weight (e.g., isocyanates, trimellitic anhydride, formaldehyde) agents. Low-molecular-weight chemicals are incomplete antigens (i.e., haptenes) that combine with a protein to produce a sensitising neoantigen. High-molecular-weight organic agents are complete sensitising antigens. The development
of occupational asthma in workers depends on many factors such as intensity of exposure, the particular sensitising agent and host factors such as atopy, cigarette smoking and genetic predisposition.16-18

5. Severe asthma: Asthma can also present in severe attacks. This type of asthma can occur at any age from childhood to adulthood and is called as severe asthma. It can be allergic or non-allergic in nature.19 Such a patient may present with near fatal attack of asthma. On detailed history, it is usually found that the patient had similar episodes in previous year for which he was admitted recurrently or a psychosocial factor may be present. Genetic factors found associated with these attacks are IL-12 promoter and RANTES-28L/G.20-22

6. Asthma with fixed airway obstruction: Approximately 35 to 50% of adult asthmatics suffer from fixed airflow obstruction instead of the normal variability seen in asthma. Sometimes this is seen even in children. It is due to airway inflammation and remodelling. Adult onset asthmatic males are generally more prone to develop fixed airflow obstruction. There is usually absence of atopy and persistent eosinophilia.23-25

7. Steroid resistant asthma: Glucocorticoids are the most effective agents in asthma treatment but some patients present with steroid resistant asthma. Steroid resistant asthma is defined as an FEV1 less than 75 percent of predicted, with failure to improve by 15 percent after an adequate dose and duration of glucocorticoid therapy (e.g., 40 mg/day of prednisolone for one to two weeks).26

8. Exercise induced asthma (EIA): When an asthmatic patient complains of bronchoconstriction after exercise, it is called as exercise induced asthma. The term exercise induced asthma is a misnomer as exercise is not an independent risk factor but acts as a trigger in asthmatic patients.27 Therefore exercise induced bronchoconstriction (EIB) is a better suited term. The magnitude of EIB is proportional to the degree of inflammation of airways. Airway inflammation is in turn measured by the number of eosinophils in airways.28,29 EIB generally manifests after 4 to 5 minutes of exercise, peaks in 10 to 15 minutes and resolves in 60 minutes. It presents as shortness of breath, chest tightness and cough. Exercise testing is usually done to confirm the diagnosis. A fall in FEV1 of more than 10% is considered to be positive.30,31

### Investigations

**Which tests are useful in a patient with asthma?**

History of recurrent episodes of airway obstruction usually after exposure to trigger factors suggests the diagnosis of asthma. Initial diagnosis is based on clinical history and investigations are done mainly to confirm the diagnosis. Pulmonary function tests are done in a patient with asthma to demonstrate reversible and variable airway obstruction. Tests to measure airway inflammation and to assess atopy are also useful in patients with asthma.

1. **To measure magnitude of airway obstruction**

These tests form the mainstay of diagnosis and assessment of severity airflow limitation in asthma.

   a. **Spirometry**

   Spirometry is used to assess severity of asthma and helps to distinguish it from chronic obstructive pulmonary disease (COPD). Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) are most common spirometric indices useful in asthma. Airway obstruction is suggested when FEV1/FVC ratio is less than 0.70. Based on values of FEV1 severity of asthma is graded as mild, moderate and severe. The visual graphical representation of obstruction is seen on flow volume loop. The expiratory limb of the loop becomes scooped and concave in cases of airway obstruction.

   In order to distinguish asthma from COPD, a bronchodilator reversibility test is performed. FEV1 values before and after inhaled short acting beta agonist (SABA) are taken. SABA is given through a nebuliser or by a meter dose inhaler (2-4 puffs) and spirometric readings are taken after 15 to 20 minutes. Sometimes anticholinergic medicines are also used. An increase in FEV1 by 12% and 200 ml from the pre-bronchodilator value indicates reversibility and supports the diagnosis of asthma.

   During remission, FEV1 and reversibility testing are normal therefore, these spirometric tests lack sensitivity. Bronchoprovocation tests are useful in such a situation.

   b. **Peak flow meter testing**

   A peak flow meter for asthmatic patient is like a thermometer for a fever patient. It helps to monitor severity of asthma.32 Peak flow meter measures peak expiratory flow rate, that is, the maximal rate at which a person can exhale during a short maximal expiratory effort after a full inspiration.
Unlike spirometry, the expiratory effort is not required to be sustained for more than 1 to 2 seconds. In outpatient department measurement of PEFR provides a quick assessment about airway obstruction. Peak flow meter is also useful for monitoring severity of asthma at home. PEFR readings are taken daily and a chart is maintained by patient for home monitoring of asthma.

Many symptomatic asthmatic patients have normal day time spirometry or PEFR performed at the time of consultation. In such patients measurement of PEFR diurnal variability is useful. It is also an indicator of severity of asthma. The patient is asked to take PEFR readings in morning and evening. Percent variability in morning and evening values is PEFR variability. It is also useful in occupational asthma. In order to prove association with a suspected allergen or trigger factor in occupational asthma, it is desirable to ask the patient to take readings at least four to five times daily and to note his daily activities and times away from work.

3. To measure Hyper-responsiveness of airways: Bronchoprovocation testing

In asthmatic patients, airway hyperresponsiveness persists even during remission. Airway hyperresponsiveness can be measured by bronchoprovocation tests (BPT). In BPT, increasing doses of a triggering substance are inhaled and FEV1 is measured. The dose at which FEV1 falls by 20% is called provocating dose 20% (PD20%). The agents used for BPT, trigger bronchoconstriction either directly or through an indirect effect. Histamine, adenosine and methacholine act directly while exercise, hyperventilation and inhaled mannitol trigger bronchoconstriction indirectly. A cut off value of methacholine PD20 is less than 8 mg/ml. It suggests a positive response for reactive airways consistent with the diagnosis of asthma. This method is useful in making diagnosis of asthma in cases of unusual presentations or when spirometry shows no airflow obstruction or reversibility.

4. To measure airway inflammation

a. Exhaled nitric oxide (FeNO)

The levels of exhaled nitric oxide are generally elevated in patients of asthma. This is due to the increase in the levels of nitric oxide synthase in the respiratory mucosa which occurs in eosinophilic inflammation. Nitric oxide synthase in turn produce increased amounts of exhaled nitric oxide (FeNO).33-36 Exhaled NO levels may also rise in association with acute airway inflammation, sputum eosinophilia, viral upper respiratory infections etc.37,38

b. Sputum tests

Sputum is induced by inhaling hypertonic saline. Sputum sample is analysed for total and differential cell counts. Higher number of eosinophils in sputum is indicator of magnitude of airway inflammation. In further analysis of induced sputum sample various cytokines and other measures of airway inflammation.

What is the role of skiagram chest and other tests done routinely?

Skiagram chest

It is usually normal in asthmatic subjects. It is used to exclude other diagnosis such as pneumonia, pneumothorax and ABPA.

Eosinophil count

The total eosinophil levels may be raised in allergic asthma. Markedly elevated eosinophil count (>15 percent or >1500 eosinophils/microL) in a patient with allergic asthma should raise suspicion for diseases like allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, Loeffler’s syndrome and tropical eosinophilia.

Total IgE

Total serum Immunoglobulin E (IgE) levels are usually elevated in allergic asthma. The levels are increased more than 1000 in ABPA. IgE estimation is also estimated in cases of moderate to severe persistent asthma in which treatment with anti-IgE monoclonal antibody is being planned.

How to identify triggers of asthma?

Clinical history is an important tool to identify trigger factors of an asthmatic patient. Allergic trigger factors can be identified by allergy tests. Allergy tests are based on the principle of presence of allergen specific IgE in the tissues. These can be performed by estimation of specific IgE in blood or by skin prick tests.

Blood tests for allergen- specific IgE

This type of test uses enzyme linked immunosorbent assay (ELISA) to detect IgE directed towards a specific allergen. The test is done for allergens suspected to be the probable triggers of asthma in an individual patient. The drawback of this test is its high cost.

Allergy skin prick test

This test is performed by a highly trained technician and involves testing a number of indoor and outdoor allergens by skin prick test. The results of this test get hampered by intake of antihistaminics and other medicines.
References