Phenotypes in Asthma

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Asthma is a heterogeneous disorder presenting with many phenotypes. Improved phenotypic characterization is necessary for linkage of specific genotypes with clinical disease manifestations. Since genotypic and phenotypic heterogeneity are inherent in asthma, patients presenting with different asthma phenotypes may need tailored therapies. The advent of targeted therapies for asthma and clinical trials based on phenotype and genotypes have raised interest in more accurate description of asthma phenotypes.

Asthma has many distinct phenotypes (“a cluster of characteristics that define a disease and its subsets”). Recognition of specific subphenotypes may further our understanding of pathophysiology, treatment response, prognosis and the underlying genetic basis for the disease. In recent years, several severe asthma phenotypes have been described. However, few studies have taken the next step to evaluate their usefulness in understanding mechanistic processes associated with asthma, improving evaluation of asthma genetics, or designing specific phenotype-driven asthma therapy trials.

In the early twentieth century, Rackemann proposed classifying asthma into ‘extrinsic’ and ‘intrinsic asthma’ based on aetiology, a concept that remains widely used. Additional asthma phenotypes based on causation have been subsequently identified, including aspirin-sensitive and occupational asthma. In the 1970s, Turner-Warwick described subgroups of patients with asthma characterized by differing patterns of airflow obstruction including ‘brittle asthma’, ‘irreversible asthma’ and ‘the morning dipper’. Ayres and colleagues later recognized two distinct subgroups of brittle asthma based on the nature of exacerbations while the concept of ‘irreversible’ asthma persists with the observation of accelerated decline in lung function leading to fixed airflow obstruction in a minority of patients.

Asthma Phenotypes Based on Trigger

1. Allergic
2. Non-allergic
3. Aspirin-exacerbated respiratory disease (AERD)
4. Infection
5. Exercise-induced

Allergic Asthma

Probably this is the most common phenotype comprising 45-88 % of asthmatic patients in recent studies. Higher prevalence is noted in children, but 60-75 % prevalence in elderly in two recent studies. This is defined based on sensitization and/or clinical correlation. Asthma risk increases with increased IgE levels and most of them are atopic.

Non-Allergic

Non-allergic, “intrinsic” asthma phenotype has long been recognized. This is asthma in patients in whom allergic sensitization is not demonstrated. There is no personal or family history of allergy.
These patients are negative for skin prick test or RAST test to a panel of seasonal and perennial allergens. IgE level is normal or low. Symptom onset is usually late. Incidence is about 10-33%

**ASPIRIN-EXACERBATED RESPIRATORY DISEASE (AERD)**

Documented asthmatic response to aspirin or other non-steroidal anti-inflammatory drug(s). Familial cases reported but relatively rare (5.5%). This is associated with HLA-DQw2 and DPB1. Genetic polymorphisms found in leukotriene C4 synthase (LTC4S), 5-lipoxygenase (5-LO), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), prostaglandin E2 receptor genes. Associated with more severe, refractory asthma, representing a major risk factor for severe asthma in outpatients. ASA may induce severe, life threatening asthma attacks. Rhinorrhea and nasal congestion are usually the first symptoms of aspirin sensitive asthma and are commonly poorly responsive to pharmacological treatment.

**INFECTION**

An individual in which a respiratory tract infection influences his/her asthma. This is associated with new onset of disease (in both children and adults), or exacerbations of the disease. Infection-induced exacerbations may be severe in nature and co-morbid condition (e.g. sinusitis) may influence asthma control.

**EXERCISE-INDUCED ASTHMA**

Most patients with asthma will develop EIB if they perform sufficient exercise to reach 80-85% of maximum predicted heart rate. EIB has been described in 7-20% of the general population. EIB is sometimes (incorrectly) thought of as a unique form of asthma, when it is seen in subjects whose disease is so mild (“mild intermittent”), that they experience bronchoconstriction only when they exercise. However, it can be seen in subjects of all ages and severities, correlating best with degree of bronchial hyperresponsiveness. Exercise-induced asthma (EIA) refers to the airway narrowing and resultant decrease in expiratory air flow that occurs following vigorous exercise.

**ASTHMA PHENOTYPES BASED ON CLINICAL PRESENTATION**

*Pre-Asthma Wheezing in Infants and Children*

Episodic (viral) wheeze: Episodic (viral) wheeze occurs at discrete time periods usually with symptoms of a viral cold, and with no wheeze between episodes.

Multi-trigger wheeze: Multiple-trigger wheeze is characterized by wheezing present with and apart from acute viral episodes. Increased number of inflammatory cells present in recurrent wheezers at 1 yr. Eosinophilic inflammation, reticular basement member (RBM) thickening & impairment in lung function are not present in first year but are present by 3 years

**EXACERBATION PRONE ASTHMA (EPR)**

Incidence in US is 500,000 hospitalizations and 2,000,000 ED Visits. Exacerbations occur in 2 groups. One group truly prone to exacerbation and in the other group exacerbation is coincidental, not predisposed. Therefore exacerbation rate is a key factor to define this phenotype.

**IRREVERSIBLE AIRFLOW LIMITATION IN ASTHMA**

This is a subgroup of asthmatics with irreversible airflow limitation or persistent airway obstruction. Limited information is available concerning this subgroup. FEV1/FVC ratio below the lower limit of normal for age and FEV1 < 90% predicted in a patient taking corticosteroids, after acute administration of a rapid onset bronchodilator

More recently, classification of asthma according to the nature of the underlying airway inflammation has been suggested ([11,12,13]) (Table 1). Importantly, new evidence is emerging to suggest that the identification of such inflammatory phenotypes may help to guide the management of asthma for individual patients.

**PHENOTYPES BASED ON INFLAMMATORY CELLS**

It is not clear whether the distinct inflammatory phenotypes occur as a result of different aetiological pathways. It is possible that this heterogeneity in inflammatory response could lead to different levels of repair and remodeling between phenotypes. This suggestion is supported by the finding of a negative correlation between sputum neutrophil count and FEV1/FVC ratio, and the absence of collagen deposition in the subreticular basement membrane in neutrophilic patients.

1. Eosinophilic: 41%
2. Neutrophilic: 20%
3. Combined eosinophilic & neutrophilic: 8%
4. Paucigranulocytic: 31%

About 41% of asthmatics have eosinophilic inflammation. Neutrophilic constitute 20%, combined eosinophilic and neutrophilic form 8% and the remaining 31% is paucigranulocytic. Subjects with eosinophilic asthma were found to produce significantly higher concentrations of sputum IL-4 than patients with noneosinophilic asthma or healthy controls, suggesting Th2 cytokine predominance. In addition, the eosinophil group produced lower levels of TNF-a than the noneosinophilic group, suggesting that treatment with agents inhibiting the TNF-a pathway may not be helpful in this group.
**Phenotypes in Asthma**

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<td>1. Pre-asthma wheezing in infants</td>
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**REFRACTORY ASTHMA**

A small proportion of patients with asthma have ‘refractory’ disease, which remains difficult to control despite usual treatment. Alveolar NO concentrations were significantly higher in patients with refractory disease and were reduced by treatment with oral but not inhaled corticosteroids, suggesting that asthma refractory to standard treatment may be characterized by distal airway inflammation. We have also shown that refractory asthma is associated with an upregulation of the tumour necrosis factor (TNF)-α axis, as demonstrated by increased expression of membrane-bound TNF-α, TNF-α receptor 1, and TNF-α converting enzyme by peripheral blood monocytes. The same patients had significantly improved measures of asthma control following a placebo controlled double-blind crossover study of treatment with soluble TNF-α receptor etanercept.

Randomized controlled trials of the monoclonal anti-IgE antibody omalizumab have shown an improvement in asthma control with reduction in exacerbation frequency in patients with symptomatic atopic asthma who had at least one positive skin-prick test and elevated serum IgE levels. Other than the presence of atopy, it is not known whether patients with a specific asthma phenotype are more likely to respond to treatment. One recent analysis of pooled data from seven studies of omalizumab suggested that patients with severe asthma characterized by persistent airflow obstruction, a need for high-dose inhaled corticosteroids and frequent asthma exacerbations were more likely to benefit, but further work linking response to clinical phenotype is required.

There is more evidence to suggest that the inflammatory phenotype predicts response to corticosteroids. The identification of an airway eosinophilia has been consistently associated with a favourable response to corticosteroid therapy in asthma and an increased risk of exacerbation following corticosteroid withdrawal. Where patients have a sputum eosinophilia despite high-dose inhaled or oral corticosteroids, the use of intramuscular triamcinolone has been shown to control the inflammation and improve symptoms. It is likely that the persistent inflammation can, at least in part, be explained by poor compliance with treatment. In contrast, noneosinophilic asthma is associated with a significantly poorer response to treatment with inhaled corticosteroids.

Asimilarlydesigned multicentre study randomized 107 patients to sputum guided or clinically guided treatment. The sputum strategy delayed the occurrence of the first exacerbation and reduced exacerbation frequency but interestingly the benefit was largely confined to patients with more severe asthma and to the prevention of eosinophilic exacerbations.

**CONCLUSION**

It is clear that asthma is a heterogenous disease with many phenotypes. Even the clinical presentation, pathophysiology and treatment response are different in different phenotypes. It will be useful to approach patient with this knowledge in mind so that treatment selection and outcome prediction are much easier.