

Clinical asthma phenotyping: A trial for bridging gaps in asthma management

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clinical characteristics, but they are now evolving to link pathophysiological mechanism to subtypes of asthma. Better characterization of those phenotypes is expected to be most useful for allocating asthma therapies. This article reviews different published researches in terms of unbiased approaches to phenotype asthma and emphasizes how the phenotyping exercise is an important step towards proper asthma treatment. It is structured into three sections; the heterogeneity of asthma, the impact of asthma heterogeneity on asthma management and different trials for phenotyping asthma.

Key words: Asthma phenotypes; Asthma heterogeneity; Endotypes; Asthma subtypes; Asthma syndrome

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Core tip: Although asthma diagnosis is based mainly on clinical basis using history taking and physical examination, treatment options are not tailored according to the clinical phenotype. We still do not have a way to work up a given patient with asthma and to easily delineate the specific pathobiology that leads to her or his airway dysfunction. We can recognize the clinical syndromes, but we cannot spell out the steps that lead from genetic or biochemical defects to disease presentation. Thus we are left with a paradox in the study of asthma; we have effective treatments that are not biologically informative, and we have informative treatments that are less effective.

Abstract

Asthma is a common disease affecting millions of people worldwide and exerting an enormous strain on health resources in many countries. Evidence is increasing that asthma is unlikely to be a single disease but rather a series of complex, overlapping individual diseases or phenotypes, each defined by its unique interaction between genetic and environmental factors. Asthma phenotypes were initially focused on combinations of

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INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by episodic reversible airway obstruction that variably presents with cough, wheezing, shortness of breath, or chest tightness^[1,2].

Asthma affects nearly 300 million people worldwide. Moreover, western countries have shown rising prevalence over the past three decades^[2]. The prevalence of bronchial asthma in the Nile Delta region of Egypt was found to be 7.7%^[3].

Asthma is a heterogeneous and genetically determined disease with different presentation, disease progression, and response to therapy. However, despite this recognition, the treatment approaches for asthma have been uniformly applied irrespective of its "subtype"^[4]. Guidelines advocate a universal stepwise approach in which medications are initially prescribed based on patient age and asthma severity, and then the number, frequency, and dose of medications are titrated upward when asthma control is inadequate.

The fact that there are some asthmatic patients with variable presentations who do not respond to commonly used medications and classified as severe asthma^[5,6], has driven the urgent need to phenotype the disease using unbiased approaches, and depending mainly on essential clinical and physiologic features for better treatment approaches.

Different researches have tried to shape asthma phenotypes through their clinical, physiologic and cellular parameters. A phenotype was defined as "observable characteristics" of subtypes of asthma ranging from clinical presentation, triggering factors to therapeutic responses. While, the fact of asthma pathogenesis is far beyond that as these different asthma phenotypes are based on different underlying biologic processes in each patient^[7].

For better understanding of this heterogeneity and the complexity of clinical and research results, the term "endotype" was evolved reflecting a specific pathogenic mechanism. Endotype was defined according to molecular pathogenesis or therapeutic responses. Thus, accurate identification of those asthma endotypes could help in tailoring of asthma therapy^[2].

ASTHMA AS A HETEROGENEOUS DISEASE

Heterogeneity of asthma reflects different clinical presentations with different responses to asthma medicines. This makes a challenge for the appropriate choice of asthma treatment. Thus, a better understanding of this heterogeneity could be of great help. Asthma heterogeneity could be explained at four levels: clinical, biological, therapeutic and molecular levels (Table 1).

Clinical level

Different studies suggest phenotypic classification

of asthma depending on clinical basis. These phenotypes include allergic and non allergic asthma. Other phenotypes defined by clinical or physiological categories (*i.e.*, severity, age at onset, and chronic airway obstruction), by asthma triggers (*i.e.*, viral, exercise, occupational allergens, or irritants), or their course (*i.e.*, early transient/persistent/late onset wheeze) have also been proposed^[8]. Other asthma phenotypes include cough variant asthma and obese asthma phenotype. Cough variant asthma was recognized as an asthma phenotype that solely presents with coughing^[9]. This asthma phenotype was defined by the presence of atopic features, milder eosinophilic airway inflammation and airway remodeling^[10].

Obese asthma phenotype is assumed to be non T helper type 2 (Th2) mediated in which low fractional exhaled nitric oxide, eosinophils and IgE levels were observed^[11,12]. Preliminary studies have suggested that in late onset obese asthma, there is increased asymmetric dimethylarginine which inhibits inducible nitric oxide synthetase leading to superoxide generation increasing the oxidative stress in such patients^[13].

Biological level

The heterogeneity of asthma as an inflammatory disorder is well established. Simpson *et al*^[14] have detected specific inflammatory endotypes in sputum samples consistent with cytokine profiles in asthmatic patients forming different endotypes that ranged from: eosinophilic, neutrophilic, mixed, and paucigranulocytic subtypes^[15]. Severe asthma was found to be a different disease entity dating since birth with a specific underlying biology^[16,17]. Thus, it should be viewed like this rather than the end result of airway remodeling. Recently, Zedan *et al*^[18] correlated clinical asthma phenotypes with the underlying cytokine and genetic pattern. Serum cytokines levels were found to be a reflection of cytokine gene polymorphisms *via* affecting the transcriptional regulation. The clinical asthma phenotypes showed statistically significant differences in cytokine profile and genotyping distribution of IL4RA-175V and IL4C-590T. Further a different genotyping was noticed when dealing with asthma as a group and after its clinical phenotyping.

Therapeutic level

In spite of asthma heterogeneity, the prescribed medications for asthma management are similar involving B2 agonists, leukotriene receptors antagonists and inhaled corticosteroids. These asthma medicines were found to control the symptoms in the majority of patients and failed in others. Several researches tried to explain this variable response to asthma therapy in different patients.

The polymorphism of $\beta 2$ receptors could adversely affect the response to regular short-acting drugs^[19]. On the other aspect, 15% of asthmatics show a reasonable response to leukotriene modifiers. However, polymorphism in 5 lipoxygenase (ALOX) and the

Table 1 Examples of proposed clinical phenotypes

	Clinical level	Clinical characteristics	Biological level	Molecular level	Therapeutic level
Xie <i>et al</i> ^[2]	Exercise induced asthma	Mild asthma and reactive bronchospasm in response to sustained exercise	Mast-cell activation; Th2 cytokines; cysteinyl leukotrienes		Responsive to cysteinyl leukotriene modifiers, beta agonists and antibody to IL-9
	Obesity asthma phenotype	Adult onset Mostly females Severe symptoms	Lack of Th2 biomarkers; oxidative stress ADMA		Responsive to weight loss, antioxidants and possibly to hormonal therapy
	Early-onset Allergic asthma	> 3 episodes per year Mild, moderate, or severe Family history of asthma	Specific IgE; Th2 cytokines; thick SBM	17q12; Th2-related genes	Corticosteroid-responsive; Th2-targeted
	Late-onset Eosinophilic asthma	Adult onset Often severe Sinus disease	Increased both peripheral eosinophils and IL-5		Responsive to antibody to IL-5 and cysteinyl leukotriene modifiers; corticosteroid-refractory
Zedan <i>et al</i> ^[8]	Shortness of breath phenotype	> 10 yr No sex predominance Longer disease duration Negative family history of asthma	Increased total serum IgE	Higher prevalence of TT genotype of SNP IL-4C 590T (Zedan <i>et al</i> ^[18])	Responsive to fluticasone alone
	Cough phenotype	< 10 yr Female predominance Shorter disease duration Positive family history of asthma	Increased both peripheral eosinophils and sECP		Responsive to montelukast alone
	Wheezy phenotype		Increase in peripheral eosinophils and sECP		Responsive to both fluticasone and montelukast

ADMA: Asymmetric dimethyl arginine; SBM: Subepithelial basement membrane; SNP: Single nucleotide polymorphism; sECP: Serum eosinophilic cationic protein; IL: Interleukin; Th2: T helper type 2.

receptor (CYSLTR2) were found to affect the drug response^[20,21].

Further, differences in corticosteroid responsiveness may be caused by complex genetic variations as more than 100 genes were found to be involved in allergic asthma, but these genetics variations are influenced by environmental exposures. Moreover, in many cases, it has been difficult to establish clear linkage because of disease heterogeneity and poorly stratified populations^[22].

By stratifying patients according to phenotype, future studies may be better able to identify the genes or other biomarkers associated with various aspects of asthma. Currently, the use of specific biomarkers to diagnose and monitor asthma is in its infancy but is being evaluated in clinical trials^[23].

Molecular level

Despite the importance of Th2 cytokines in atopic asthma, recent data in both adults and children has challenged the concept of a Th1/Th2 imbalance and has showed an evidence of Th1 profile.

Th2 imprint was present in only 50% of the mild asthmatics and those patients were characterized by lung eosinophils, mast cells, higher IgE levels, hyperreactive airway, higher tissue expression of Th2 cytokines and thicker subepithelial basement membrane^[24,25]. In addition, they showed a good response to inhaled corticosteroids in contrast to those

without the type-2 cytokine profile.

IMPACT OF ASTHMA HETEROGENEITY ON ASTHMA MANAGEMENT

Asthma therapy can markedly improve quality of life, morbidity, and mortality of asthma patients and decrease health care costs if applied to the right patient at the right time^[26]. The choice of controller medications should be based on clinical efficacy, patient phenotype, previous responses to treatment, patient's compliance, side effects, and drug safety^[27].

Although asthma diagnosis is based mainly on clinical basis using history taking and physical examination^[28], treatment options are not tailored according to the clinical phenotype. We still do not have a way to work up a given patient with asthma and to easily delineate the specific pathobiology that leads to her or his airway dysfunction. We can recognize the clinical syndromes, but we cannot spell out the steps that lead from genetic or biochemical defects to disease presentation. Thus we are challenged by a paradox in the management of asthma; we have effective treatments that are not biologically informative, and we have informative treatments that are less effective^[29].

Recently, the new emerging cytokine based therapies flare the importance of asthma phenotyping. Effective application of these new therapies to certain patients depends on the development of biomarkers of

molecular heterogeneity in asthma^[30].

DIFFERENT TRIALS FOR ASTHMA PHENOTYPING

A phenotype is defined as the “observable properties of an organism that are produced by the interactions of the genotype and the environment”^[31]. Multiple approaches have been proposed for asthma phenotyping, none has been widely agreed upon. Many of those approaches have been biased; depends mainly on clinical characteristics without obvious inflammatory biomarkers. Also, the selection of a single dominant characteristic to categorize a given patient is mostly inaccurate as it ignores the overlap between groups^[32]. These include categorization of patients based upon atopic state, symptomatic trigger, disease severity, and pattern of airflow obstruction. In addition, pathological classifications, despite being important for clarifying disease pathogenesis, they are extremely invasive clinically.

Several studies have approached asthma phenotyping in a less biased and more statistically based manner^[31] as a result of lacking of specific biomarkers for each asthma phenotype. Three large clinically oriented analyses performed in Europe^[33,34] and the United States^[35,36] developed clusters based upon age of onset of asthma, gender, allergic features, asthma symptoms, and lung function as well as other factors that varied between the three studies. The resulting phenotypes include early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations.

Four clusters were identified based upon asthma duration, the number of asthma controller medications, baseline Forced Expiratory Volume in 1 s, skin test, and total serum IgE. All of them were strongly associated with histories of atopic dermatitis and atopy, although the degree of atopy as measured by number of positive allergy skin tests and total serum IgE did differ significantly between groups^[34]. However, these studies lacked the accurate pathological and immunological definition of asthma phenotypes^[31].

Asthma has a strong genetic component^[37]. Most of genetic association studies have dealt with asthma as a one disease^[38] and only few studies^[39] delineated specific asthma phenotypes. Asthma subtypes cannot be termed phenotypes without linking the observable characteristics to the genetic signature of the patients^[40]. Woodruff *et al.*^[41] began to identify molecular phenotypes of asthma. They analyzed airway epithelial brushings and they identified “TH2 high” and “TH2 low” individuals.

Zedan *et al.*^[27] proposed three clinical asthma phenotypes based on symptomatology after validation of these symptoms^[42,43]. The study tried to characterize three clinical phenotypes [shortness of breath (SOB), cough, and wheeze] by specific inflammatory bio-

markers and their response to asthma medications. They found that children who had SOB had older age, and longer disease duration, higher levels of total serum IgE, and responded to fluticasone alone. While cough group was found to have younger age, shorter disease duration, higher levels of eosinophilic% and serum Eosinophilic Cationic Protein, and responded to montelukast alone. Moreover, wheezy group showed mixed pattern and responded to both medications^[27].

Two single nucleotide polymorphisms (SNPs) in IL-4 and IL4RA were studied in Egyptian asthmatics with different clinical phenotypes^[18]. They found that asthma as a group had AG heterozygosity genotype, whereas cough with SOB group showed AA and GG homozygosity genotype. In addition, cough group and SOB group revealed significant increase in serum levels of IL-17 among patients with CC homozygote variant of IL-4C 590T compared to patients with CT heterozygote variant. In turn, phenotyping based on symptomatology makes a sense in endotyping of asthma, which may have a reflection on heterogeneity in response to asthma medications^[18].

The previously mentioned clinical asthma phenotypes were found to express a significant value in detection of specific cytokine and genotype profiles for asthma; hence this may help in prediction and diagnosis of clinical asthma phenotypes which might have a potential value in tailoring asthma therapies.

The concept of personalized medicine, however, gained most traction from the application of genetics to patients with disease. Polymorphisms in genes (both single nucleotide polymorphisms, SNPs, and other more substantive coding variations) are associated with therapeutic responses to short-acting beta2 agonists, leukotriene inhibitors, corticosteroids, and several others; other polymorphisms confer risk of developing diseases: asthma, atopy, bronchial hyperresponsiveness, *etc*^[44].

CONCLUSION

Asthma is a complex disease with evidenced heterogeneity at different levels. Despite this heterogeneous nature, the same treatment approaches are still applied for different patients with variable responses. Phenotyping/endotyping dilemma is the only roadmap to bridge the gap between this variable disease and the single approach of management. A key obstacle in this field is a lack of “gold standard” phenotypes with underlying identifiable biomarkers, genetic, or molecular profiles. A novel conceptual framework to link the clinical signature of every patient to her/his inflammatory phenotype is very essential to meet the challenges of tailoring the right medications for to the right patient at the right time.

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