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Asthma Heterogeneity and Severity – Why is Comprehensive Phenotyping Important?

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Asthma is characterized by heterogeneity and variability in expression[A: of what?] that is present throughout the asthma spectrum but is most evident in more severe disease phenotypes. Understanding the clinical characteristics as well as the genetic and biologic mechanisms responsible for disease heterogeneity and progression will provide insight into asthma pathogenesis and is important for disease management and the development of personalized therapeutic approaches. Many subphenotypes of severe asthma have been described based on physiologic parameters (chronic airflow obstruction), historical events (exacerbation rate, age of disease onset), inflammatory markers (Th1 and Th2 predominant, sputum eosinophilia) or multivariate phenotypes using cluster analysis. In 2013, there were several reports focused on the pathobiologic or genetic basis of asthma heterogeneity and severity.²⁻⁸ Investigators explored asthma subphenotypes utilizing more invasive profiling with specialized quantitative computed tomography (CT) scanning or bronchoscopy and mucosal biopsy.^{2,3} Others expanded and refined inflammatory cellular assessments, evaluated the influence of obesity and studied the role of peripheral airway obstruction.^{3-5,8} Each of the reports discussed below improves our understanding of severe asthma subphenotypes. These comprehensive approaches will augment our ability to individualize asthma therapy in the future.⁹⁻¹¹

Quantitative computed tomography (CT) is a newer methodology that directly measures the thickness and size of the segmental airways and indirectly assesses the small airways by estimating air trapping and hyperinflation. A recent study by Gupta and coworkers explored heterogeneity in proximal airway wall structure (thickness and luminal area) and hyperinflation related to airflow obstruction (lung density score) in more severe asthma and described three clusters of subjects that were differentiated by these measures.² While different degrees of hyperinflation were found in all three groups, patients in the two more severe clusters had different airway lumen sizes; segmental airways in one group were “dilated” (similar to bronchiectasis) while airways in the other group were “narrowed” or constricted. While not significant (likely due to the small sample size), there was more

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hyperinflation, more severe airflow obstruction and less responsiveness to bronchodilators in the “dilated” group showing phenotypic similarities to COPD. The “narrowed” group, in contrast, had higher body mass indices (BMI) and airflow limitation that improved with beta-agonist administration. Sputum eosinophil measurements were higher in the “narrowed” obese group although not significantly different. These findings have implications about obesity in asthma suggesting that obesity is not only related to mechanical effects on lung and airway function but may also be characterized by persistent eosinophilic airway inflammation.

Initial descriptions of obese asthma phenotypes focused on the physiologic consequences of increased chest wall restriction and decreased expiratory reserve volume and characterized the obese asthma patient as a nonatopic and non-inflammatory subphenotype.¹² While functional changes in respiratory mechanics impact asthma symptoms and quality of life, more recent analyses have focused on whether obesity alters the “traditional” allergic or non-allergic pathobiologic mechanisms associated with asthma. An important article by Desai and colleagues this year addresses the role of the eosinophil in late-onset obese severe asthma patients using blood, sputum and bronchial biopsy samples.³ There was no difference in blood or sputum eosinophils among three asthma groups stratified by BMI, however, sputum IL-5 levels were highest in the more obese asthma group. In a smaller cohort that underwent bronchial biopsy, submucosal eosinophils were positively correlated with BMI, although there was significant heterogeneity. Together these results imply that there is a subgroup of obese patients with severe asthma that have persistent submucosal eosinophilia despite exposure to high doses of inhaled or oral corticosteroids. There was no difference in the frequency of atopy or serum IgE levels among the asthma groups suggesting that Th2 inflammatory mechanisms and eosinophils are still important in the subset of patients with co-existing obesity and severe adult onset disease.

Many studies in asthma have emphasized the importance of Th2 inflammation and have characterized these patients as persistently “eosinophilic” or “noneosinophilic” despite appropriate anti-inflammatory therapies. Recently, there has been increasing interest in the importance of the neutrophil in asthma and several publications have concurrently stratified both granulocytes into four categories of airway inflammation (paucigranulocytic, eosinophil predominant, neutrophil predominant and mixed granulocytic).^{4,5,8} A recent analysis in a large cohort by Schleich and coworkers likewise showed that the subjects with a neutrophilic or mixed granulocytic sputum profile had the most severe asthma.⁴ The importance of the neutrophil in severe asthma was further confirmed by a new unbiased cluster analysis performed by the NIH Severe Asthma Research Program.⁵ Nearly all asthma subjects in the more severe cluster groups had elevated sputum neutrophils (83-97%) and over one third (34-45%) had concurrent elevations in sputum eosinophils or a mixed granulocytic inflammatory profile. Thus if only eosinophilic phenotypes had been evaluated some of these severe asthmatics would have been identified as only eosinophilic, but the potentially important neutrophilic component would have been ignored. Together these results imply that neutrophils may be an important biomarker or effector cell for severe asthma, but also that persistence of airway eosinophilia in addition to neutrophilia may be a fundamental finding in subjects with the most severe asthma.

These publications offer novel observations that need to be incorporated into comprehensive assessment of asthma phenotypes. The need for careful comprehensive phenotype assessment is not limited to the evaluation of asthmatics as candidates for treatment with newer biologic therapies; it is important in understanding pathophysiologic mechanisms in asthma subpopulations. Genetic approaches in asthma are now focused on understanding mechanisms responsible for disease progression, heterogeneity and severity. Recent genome wide association studies (GWAS) in asthma have identified a severe exacerbation locus and lung function genes that include novel Th1 pathway genes.^{6,7} Combining genomic, molecular biologic and comprehensive phenotyping (“phenomics”) with systems biology methodology will characterize disease heterogeneity in severe asthma using evidence based criteria. These translational scientific approaches will form the basis for precision medicine and individualized therapeutics in severe asthma.

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