Changes in Phenotype of Childhood Wheezing and Asthma

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Introduction

Asthma is a complex clinical syndrome characterized by variable airflow obstruction, airway hyperresponsiveness, and cellular inflammation. Many attempts have been made to classify asthma on the basis of clinical features and to correlate these characteristics with pathologic findings.

Classifications of asthma phenotypes

Early attempts at phenotyping asthma focused on extrinsic versus intrinsic asthma. Other methods of classifying asthma based on a single clinical or demographic variable have included early-onset versus late-onset asthma and exercise-induced asthma; however, these have been poorly characterized and lack supporting longitudinal studies.

Wheezing in early life was studied in the longitudinal Tucson Children's Respiratory Study (TCRS). The researchers followed newborns for wheezing episodes in the first 3 years and classified three phenotypes based on their time of onset and duration in chronic cases (transient, persistent, and late onset). Another birth cohort study, the British Avon Longitudinal Study of Parents and Children (ALSPAC) added two different phenotypes to those of the TCRS: intermediate-onset wheeze and early prolonged wheeze. These clinical phenotypes frequently overlap and can change over time.

Newer approaches to characterizing asthma phenotypes

1) Inflammatory phenotypes

A study in 2006 examining eosinophil and neutrophil percentages in induced sputum found four inflammatory subtypes of asthma: eosinophilic, neutrophilic, mixed granulocytic, and pauci-granulocytic asthma. There has been longstanding evidence that patients with eosinophilic asthma (>2% eosinophils in sputum) exhibit a greater responsiveness to steroids than those with neutrophilic asthma.

2) Cluster analysis

Cluster analysis is a new, less biased, statistical method that attempts to cluster patients by a wide range of preselected variables, such as age of onset, atopy, sex, severity of obstruction, and others. A cluster analysis of the Severe Asthma Research Program (SARP) data was published in 2011. The researchers used 12 variables and identified four clusters of severe asthma in children.

Moving beyond asthma phenotypes

1) Genome-wide association studies

Genome-wide association studies (GWASs) have identified several genetic loci that might influence asthma susceptibility. The first GWAS on asthma, published in 2007, found that ORMDL3, located on chromosome 17q21, was a potential asthma candidate gene. This approach significantly improved our understanding of the etiology of asthma and led to better classification of asthma phenotypes.

2) Epigenetic phenotypes

Epigenetics may explain how genetic susceptibility and exposure to environmental factors interact in defining atopic disease phenotypes. Methylation is the most extensively studied epigenetic mechanism in asthma-related genes and environmental effects. Altered histone modifications and aberrant expression of micro-RNAs might also play a role in asthma.

Conclusion

The current hope is that a better understanding of asthma heterogeneity will allow us to select treatments based

on the greatest likelihood of therapeutic response, thereby improving asthma control and quality of life for patients.

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