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Asthma in childhood: a complex, heterogeneous disease

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Asthma in childhood is a heterogeneous disease with different phenotypes and variable clinical manifestations, which depend on the age, gender, genetic background, and environmental influences of the patients. Several longitudinal studies have been conducted to classify the phenotypes of childhood asthma, on the basis of the symptoms, triggers of wheezing illness, or pathophysiological features of the disease. These studies have provided us with important information about the different wheezing phenotypes in young children and about potential mechanisms and risk factors for the development of chronic asthma. The goal of these studies was to provide a better insight into the causes and natural course of childhood asthma. It is well-known that complicated interactions between genes and environmental factors contribute to the development of asthma. Because childhood is a period of rapid growth in both the lungs and the immune system, developmental factors should be considered in the pathogenesis of childhood asthma. The pulmonary system continues to grow and develop until linear growth is completed. Longitudinal studies have reported significant age-related immune development during postnatal early life. These observations suggest that the phenotypes of childhood asthma vary among children and also in an individual child over time. Improved classification of heterogeneous conditions of the disease will help determine novel strategies for primary and secondary prevention and for the development of individualized treatment for childhood asthma.

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Introduction

Asthma in children is a heterogeneous disease comprising different phenotypes[1]. Wheezing, a non-specific sign of airflow restriction in narrowed airways, is a major clinical expression of childhood asthma. Furthermore, many different conditions have been reported to be associated with lower airway obstruction during childhood[2]. All these factors complicate our understanding of the pathogenesis and natural course of childhood asthma.

It is well-known that a complex interplay between genetic predisposition and environmental influences contributes to the development of asthma. However, in the pathogenesis of childhood

asthma, developmental factors should be considered, including factors related both to the lungs and immune system[3]. Childhood is a period of rapid growth and pronounced changes in the pulmonary and immune systems. Longitudinal studies on the development of the immune system have shown a significant age-related development during postnatal early life difference during early life[4-6]. Our previous study showed significant developmental changes in cytokine responses during the early years of life[7]. We also observed significant age-related differences in interferon (IFN)-γ and interleukin (IL)-13 responses in children with acute respiratory syncytial virus (RSV) bronchiolitis[7].

Lung development is a process that begins in the 4th week of gestation and continues for a significant period after birth[8, 9]. Alveolar multiplication, the final stage of lung differentiation, begins at term and continues for the first 2-3 years of life[8]. The lungs grows throughout childhood, and the development of lung function roughly parallels the increase in height, which continues until adolescence, when the linear growth is completed[9, 10].

Collectively, these observations suggest that the phenotypes of childhood asthma vary among children depending upon their age, gender, genetic backgrounds, and environmental exposure, and vary within an individual child over time.

Clinical findings in major epidemiologic studies

Several major epidemiologic studies have provided information about the clinical course of childhood asthma as children age. The first study was the Melbourne Asthma Study that started in 1967. Children with asthma and a set of normal individuals were enrolled at age 7 and followed at age 10, 14, 21, 28, 35, and 42[11-13]. This cohort study showed that asthma symptoms improved by adolescence, but many relapsed as they aged into adulthood. Children with infrequent wheezing usually outgrew their asthma by early adolescence, while those with more severe symptoms continued to have persistent asthma. This same cohort demonstrated that those children with "severe asthma" presented decreased lung function, which did not improve with age but did not decrease further when they became adults. The study suggests that some asthmatic children are either born with reduced lung function or they lose lung function during the first few years, before 7 years of age, after which no further loss occurs. Sears et al. evaluated a birth cohort that started in 1972 in New Zealand and followed up on 7 occasions from age 9 to 26[14]. At 26 years of age, of the 613 subjects who had complete data, 26.9% were still wheezing, 14.5% had persistent wheezing from onset, and 12.4% presented a remission followed by relapse. The risk factors for persistent or relapsing wheezing were greater bronchial hyper-responsiveness, sensitization to house dust mites, female gender, exposure to tobacco smoke, and early start of wheezing. These findings strongly suggest that the interaction, during early life, between environmental factors and asthma-specific genetic factors is crucial in the development of later asthma in the wheezy infants.

The Childhood Asthma Management Program (CAMP) is the largest and longest clinical trial in children with mild to moderate asthma diagnosed by the current asthma guidelines[15]. The CAMP study has now evolved into an epidemiological study of the natural course of childhood asthma. The study has shown that longer duration of asthma in these patients was significantly correlated with a greater degree of airway hyper-responsiveness and significant effects on lung growth, which is consistent with the previous longitudinal studies. However, the percentage of CAMP participants with an abnormally low FEV_1/FVC ratio increased with age, signaling progressive effects of asthma on lung function in adolescence, which differs from findings in the previous studies.

Longitudinal epidemiological studies have shown that early childhood asthma generally improves during adolescence and young adulthood. They also indicate that, the more severe asthma is in childhood, the less likely it is that remission will occur. Decreased lung function occurs early and does not change further with aging; however, the CAMP cohort showed a progressive effect of persistent asthma on lung function during adolescence. These studies suggest that early diagnosis and intervention are needed to reduce adverse outcomes of childhood asthma.

Different asthma phenotypes in childhood

It is well known that there are different patterns of wheezing in young children, probably with some superposition between them. The classic epidemiological phenotypes were described in the Tucson study, based on the time of onset and persistence of symptoms[1,16]. These findings were amplified in the Avon Longitudinal Study of Parents and Children[17].

The Tucson study proposed 3 classical phenotypes of childhood wheezing or asthma: transient early wheezers, non-atopic wheezers, and persistent atopic wheezers/asthmatics. Transient wheezers have wheeze-related symptoms only during the first 3 years of life, which resolve between the ages of 3 and 6. This phenotype is not commonly associated with a familial and/or personal atopy or asthma. They have reduced lung function diagnosed shortly after birth before any event of respiratory illness, which remains decreased until 22 years of age[18]. Structural or functional changes in airways, such as reduced airway resistance or increased compliance, would predispose these subjects to wheeze easily when they have respiratory infections and other risk

factors such as exposure to tobacco smoke.

The non-atopic wheezer group comprises children whose wheezing starts in late infancy or at preschool age and continues beyond 6 years of age, but has a tendency to disappear pre-adolescence. These children have slightly lower lung function compared with non-wheezing healthy subjects. The principal factor that triggers wheezing in this group is acute respiratory infection, and many studies have explored the relationship between viral infection and asthma. Stein et al. demonstrated, in a longitudinal study, that children who had RSV infection during the 1st 3 years of life had a greater risk of having a persistent wheeze up to 11 years of age[19]. They are more likely to have lower lung function but this is not associated with increased risk for atopic sensitization.

The third phenotype, persistent atopic wheezers/asthmatics, is composed of the children whose symptoms started during the 1st 3 years of life and continue during school age and adolescence [1]. These children have a familial history of atopy, and early allergic sensitization. There is a significant association between an early onset of wheezing and disease severity and airway hyper-responsiveness. Moreover, early allergic sensitization to aeroallergens has been shown to be predictive of persistent wheeze or asthma, airway hyper-responsiveness, and loss of lung function.

The Avon Longitudinal Study is a birth cohort study, which enrolled 6,265 children from birth and followed them at 6, 18, 30, 42, 54, 69, and 81 months of age[17]. Five phenotypes of wheeze were defined by the estimated prevalence of wheezing at each time point: transient early wheeze, prolonged early wheeze, intermediate onset wheeze, late onset wheeze, and persistent wheeze. Although the phenotypes have similarities to those previously reported, there were differences in their associations with objective outcomes. Intermediate and late onset phenotypes had the strongest associations with atopy, which may present in the critical period during which environmental factors such as allergens or viral infections interact with genetic predisposition to influence the risk of developing asthma[17].

Early virus-induced wheezing and childhood asthma

Most children with asthma experience their first episode of wheezing during early childhood and those initial insults are usually caused by viral respiratory infections. This relationship has been suggested in many epidemiological studies, which have shown the natural history of asthma and age-related changes in asthma phenotypes. The first years of life are a period of rapid growth and development in the immune and pulmonary systems and delicate regulation of these developmental processes. It is likely that the effect of an acute inflammatory response to respiratory infection on immature lung structure and function might be associated with the long-term consequences of infection. However, the question of whether viral respiratory infection is a causal factor or an indicator of a predisposition to asthma is still not resolved. RSV is the most common pathogen causing bronchiolitis during infancy and has been most widely studied in connection with its relationship with subsequent childhood asthma. A previous long-term follow-up study has shown that severe RSV bronchiolitis in infancy is an independent risk factor for asthma up to age 13[20, 21]. Another follow-up study to age 13, which showed debatable findings, reported that RSV bronchiolitis in the first 3 years of life was associated with frequent wheezing up to age 11, but no longer at age 13, and that this association was not caused by an increased risk of allergic sensitization[19]. The authors suggest that RSV bronchiolitis itself is not a risk factor for the development of atopic asthma. This discrepancy might be explained by the fact that the infants enrolled in the first study were those with severe RSV bronchiolitis who needed hospitalization, while the second one was part of a population-based study. These findings are supported by a recent study showing a dose-response relationship between the severity of infant bronchiolitis and early childhood asthma[22]. Moreover, a recent study suggested that RSV infections severe enough to result in hospitalization are an indicator of genetic predisposition, rather than a causative factor[23]. There has also been a study that demonstrated a significant association between RSV-induced wheezing and persistent wheeze at 5 years of age, only in children with early atopic sensitization[24]. An interesting study once proposed a possible genetic link between atopy and the severity of RSV infection; a common IL-4 haplotype has been shown to be associated with increased IL-4 transcription and predisposition to asthma[25]. Choi et al. reported that a particular IL-4 gene haplotype, which is associated with increased IL-4 transcription and predisposition to asthma, is associated with severe RSV bronchiolitis in Korean children[25].

Collectively, childhood asthma is a complex disease presenting heterogeneous wheezing phenotypes, which might be dependent upon the interaction of genetic and environmental factors.

Asthmatic children with airway remodeling

Many children outgrow their preschool wheeze, but others have persistent symptoms and go on to develop asthma. Structural changes to the airway, airway remodeling, play an important role in the pathophysiology of asthma. Thickening of the reticular basement membrane (RBM) of the airway epithelium is a characteristic finding of remodeling, which is relatively well proven in adults by bronchoscopic examination. A few studies have shown these

characteristic features of adult asthma in school-aged children[26, 27]. Although such a study is not easily available in young children, there has been a series of reports showing that RBM thickening and eosinophilic inflammation have not yet started to develop at 12 months, but have started developing by 30 months of age[28, 29]. These previous studies suggest that there might be a critical time for intervention to modify the natural course of childhood asthma.

Recent studies have suggested that airway remodeling is a consequence of repeated injury and persistent inflammation of the airway epithelium[30]. Repeated virus-induced wheezing in early childhood has been shown to predict adult asthma[31]. We observed previously that significantly increased vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor (PAI)-1, important mediators in the process of structural changes to airways, are present in children with recurrent early wheeze[32]. Moreover, a recent study showed significantly increased levels of epidermal growth factor (EGF) and amphiregulin during acute asthma exacerbation[33], which suggests that airway remodeling processes might progress with every acute attack and contribute to the development of chronic asthma. Prevention and appropriate management of recurrent asthma attacks may be crucial to prevent progressive structural changes in asthmatic children.

Conclusion

Asthma is not a single disease entity, but incorporates a number of clinical syndromes. There has been a continuous need for the identification of clinically relevant phenotypes of asthma, particularly during childhood, when many of the major influences on asthma development start. Improved classification of asthma phenotypes in children is expected to increase our understanding of the etiology and natural history of wheezing illnesses in childhood. This will make it possible to find novel strategies for primary and secondary prevention of disease in specific subgroups and also to develop phenotype-specific treatment of asthma.

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