KAAACI Symposium 1: Pediatric asthma

Asthma in childhood and adolescence: remission or progression?

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Abstract

There are different perspectives whether adult-asthma are originated from childhood asthma or are newly developed adult-onset asthma, between pediatric and adult allergist. Asthma is a typical non-communicable disease that begins in early childhood and can be chronic life-long burden for many people. The underlying cause of asthma is a complex product of genetic and environmental factors resulting in significant heterogeneity of the disease. These complex-interaction make asthma to show various phenotypes and natural course. Most children with early life wheezing may outgrow their symptoms during school years, but asthma relapses are common in young adults. In addition, early impaired lung function may continue to adulthood. Previous studies on the asthma transition from childhood into adult are largely heterogeneous. Remission is common in the mild wheezy infant, but uncommon in children with severe asthma, AHR, or impaired lung function. In this presentation, I will summarize the current available prospective data on the transition of childhood asthma into adulthood, particularly early-childhood wheezing, and risk factors for the asthma-persistence or relapse later in life.

Introduction

Asthma is a typical non-communicable disease that begins in early childhood and can be chronic life-long burden for many people. In recent decades, it has become the most prevalent respiratory, allergic disease in childhood. The etiology of asthma has been considered to a result of genetic, epigenetic, developmental, and environmental factors, along with their complex interactions.[1] The underlying cause of asthma is a complex

product of genetic and environmental factors resulting in significant heterogeneity of the disease. These complex-interaction make asthma to show various phenotypes and natural course. Wheezy infants are also heterogeneous group with different phenotypes and natural course. One-third of children suffers from wheezy illness before age 3, but most of them are known to remit their symptoms by school age and adolescence. However, remission of symptom does not mean cure of asthma. In fact, airway hyper-responsiveness (AHR) and airway inflammation might remain despite remissions of symptoms. In addition, recent long-term post-bronchiolitis studies have reported that asthma is present in approximately 40% of young adults who have history of hospitalized bronchiolitis, and over half of adult-asthma are relapses after symptom-free years. There are different perspectives whether adult-asthma are originated from childhood asthma or are newly developed adult-onset asthma, between pediatric and adult allergist.

Asthma transition over time from childhood into adulthood

It is widely reported that approximately 80% of children with asthma present wheezing in the first few years of life, whereas about 30% of early wheezing develop asthma.[2-4] About 35% of childhood asthma remits during school age.[5] It is known that asthma is a heterogeneous entity whose manifestations vary with age. Up to 30% of asthma experience remission for $\geq$ 4 years up to age 26.[6] The Childhood Asthma Prevention Study (CAPS) cohort, are randomized clinical trial investigating the effectiveness of a house dust mite avoidance and ω-3 fatty acid supplementation in high-risk births up to age 5 for the primary prevention of asthma. CAPS showed that the transition probabilities of moving phenotype to another phenotype were common in childhood. Transitioning probability between ages 1.5 and 3 years was 12% (range 0-47%), but less common in later childhood.[7] The Melbourne Asthma Study (MAS) cohort explored transitions of asthma-severity over time from childhood into adulthood. Wheezy bronchitis or mild asthma showed a trend for transition into remission, whereas severe asthma remained severe asthma.[8] Asthma remission is known to be associated with male, mild severity, and no smoking. Unfortunately, considerable proportion of asthma with remission may relapse later in life. With regarding to asthma transition, most arising questions are about remission and relapse of childhood asthma in adulthood, and risk factors for persistence and relapse, and cause of adult-onset asthma.

Dose most of childhood-asthma remit up to adolescence?

Remission rate in cohort studies

The British 1958 birth cohort showed that about 50% of those with prior asthma or wheezy bronchitis remitted at age 7, 81.8% at age 11, 89.8% at age 16, 90.3% at age 23, and 72.6% at age 33.[9] The Tasmanian asthma cohort showed about 75% of remission rate up to age 25.[10] The MAS showed that

remission rates were 72.7% in wheezy bronchitis, 30% in asthma, and 10% in severe asthma at age 35, but this rate slightly increased at age 50 with 64% of wheezy bronchitis, 47% of asthma, and 15% of severe asthma.[11,12] The Dunedin Multidisciplinary Health and Development Study (DMHDS) showed that remission rate was 38.6% during follow-up age 3 to 18 years, and 27.4% at age 26.[6,13]

Remission rate in clinical studies

The Childhood Asthma Management Program (CAMP) reported about 6% of remission rate by age 18.[14,15] The participants in the CAMP study, were mild to moderate asthma with persistent asthma symptoms with peak flow less than 80% of personal best and $PC_{20} \leq 12.5$ mg/mL. This low remission rate might be due to the fact that previous observational studies have relied on the patients od parents' recall, but CAMP study frequently interviewed and identified the status of asthma. Another clinical study, Dutch clinical study, showed higher remission rate than CAMP study. The remission-rate up to age 32-42 was 51.7%, and complete remission with negative AHR was 22.0 %. However, the authors presented that some of participants might be transient wheeze or not asthma.[16]

Remission rate in postbronchiolitis studies

Up to date, there are only two prospective longitudinal postbronchiolitis studies have followed-up to adulthood.[17-20] In these studies, over half of patients who were hospitalized bronchiolitis, have suffered from recurrent wheezing by age 3, 25-54% at age 4-6, 15-30% at age 7-10, and 30-43% at age 17-20. These findings showed that children with recurrent wheezing outgrowed their symptoms during school age, but became symptomatic again in adulthood often after many symptom-free years.

Relapse rate

The British 1958 birth cohort showed that about 28% of asthma with remission relapsed in adulthood after a period of remission during late teenage years.[9] MAS cohort also showed a considerable relapsing rate as approximately 30%.[11,12] The DMHDS demonstrated that about 30% of those with prior asthma-remission at 18 years of age experienced relapse by age 26, particularly in 60.7% of asymptomatic AHR were relapsed up to age 26.[13]

As Table 1 shows, most children with asthma or recurrent wheezing remit asthma-symptoms during adolescence and early adulthood in cohort studies including questionnaire-based recurrent wheezing.[9,10] Whereas, most children have failed to meet remission during same period in clinical asthma studies.

Table 1. Remission and relapse rate of childhood asthma

	Country	Sample size	Age at enrollment, years	Age at follow-up, years	Remission rate	Relapsing rate	Definition
Prospective birth cohort studies							
*PIAF cohort[29]	Australia	253	0	24	43%	na	Questionnaire; physician diagnosed asthma Remission; no symptoms or asthma medication use in the previous 12 months
British 1958 Birth Cohort[9]	UK	880	0	33	49.8% at age 7 81.8% at age 11 89.8% at age 16 90.3% at age 23 72.6% at age 33	27.4%	Interview; wheezy bronchitis or asthma (asthma- ever up to age 7)
Prospective longitudinal studies, not birth cohort							
† OLDNS Study[31]	Sweden	248	7 to 8	19	21%	na	Asthma; ISAAC questionnaire Remission; no use of asthma medication and no wheezing during the past 12 months
‡ MAS[11,12]	Australia	484	7	35	72.7% of wheezy bronchitis, 30% of asthma, 10% of severe asthma	na	Remission; no wheeze symptoms and no use of asthma medication in the past 3 years, direct telephone interview Wheezy bronchitis; ≥ 5 episodes of wheezing related respiratory infections
				50	64% of wheezy bronchitis, 47% of asthma, 15% of severe asthma		Asthma; wheezing not associated with respiratory infection Severe asthma; onset < 3 years of age, and > 10 attacks in the 2 years, and FEV1/FVC ratio < 50%
∫ DMHDS[6,13]	New Zealand	1037	3	18	38.6%	35.3%	Questionnaire based
				26	27.4%	12.4	Remission: absence of wheezing at least 2 years Relapse: current wheezing
Tasmanian asthma survey[10]	Australia	1.000	7	25	74.4%	na	Questionnaire
Clinical study							
Dutch study[16]	Netherlands	119	5-14	32-42	51.7% - 22.0% complete remission - 29.7% clinical remission	na	At enrollment: physician diagnosed asthma with 80% of positive AHR. Complete remission: none of all; asthma symptoms, ICS-use, FEV_1 ≤90%, and AHR (PC_{20}≤16 mg/mL) Clinical remission: none of asthma symptoms or ICS-use
‖ CAMP study[14,15]	USA	1041	5 to 12	18	6%	na	At enrollment: mild to moderate asthma with persistent asthma symptoms, peak flow less than 80% of personal best, and PC20 ≤ 12.5 mg/mL

*PIAF cohort, Perth Infant Asthma Follow-up cohort
† OLDNS Study, The Obstructive Lung Disease in Northern Sweden study
‡ MAS, Melbourne Asthma Study
∫ DMHDS, The Dunedin Multidisciplinary Health and Development Study
‖ CAMP, The Childhood Asthma Management Program

Does remission of asthma symptoms mean remission of underlying airway pathology?

Airway hyper-responsiveness

The DMHDS cohort showed that 34.9% of those with clinical remission were AHR positive (PC20≤ 8mg/mL), and particularly in 60.7% of asymptomatic AHR were relapsed up to age 26.[13] Dutch clinical cohort showed that 575 of subjects in clinical remission had AHR.[16] In a clinical setting, adolescent in clinical remission of atopic asthma showed responsiveness to both adenosine 5'-monophosphate and methacholine were higher than healthy control, whereas lower than current asthma.[21]

Airway inflammation, and remodeling

Van den Toorn et al,[21] reported that adolescent in clinical remission of atopic asthma showed significantly higher exhaled nitric oxide than healthy control (18.9 vs. 1,0 ppb), but similar level with current asthma (18.9 vs. 21.9 ppb). The authors suggested that persistent airway inflammation during clinical remission of atopic asthma. As a follow-up study, the authors studied to investigate whether atopic asthma in remission have persistent airway inflammation or airway remodeling. Clinical remission defined as neither asthma-symptoms nor use of asthma medications within 12 months, and fifty-four subjects who aged 18 to 25 years were recruited. Among them, 18 subjects with clinical remission showed persistent airway inflammation and airway remodeling. Importantly, the degree of remodeling was similar to that of current asthma.[22] They suggested ongoing inflammation and airway remodeling in adolescent in clinical remission of atopic asthma.

Taken together, whether clinical remission of asthma-symptoms equals the remission of underlying airway pathology is still unclear. However, the evidences have shown that AHR and airway inflammation might remain despite the absence of asthma-symptoms. Symptom remission does not reflect remission of underlying airway pathology.

Risk factors for persistence, relapse, and adult-onset of asthma in adult life

Persistence

Early diagnosis and treatment were emphasized to prevent or modify the natural course of asthma. However, CAMP's land-mark study showed that early treatment of childhood asthma could not change the natural course and impaired lung function.[23] The CAMP study showed that children with asthma were remitting (6%), periodic (39%), and persistence (55%) nevertheless use of anti-inflammatory treatment,[14] FEV1/FVC ratio decreased over time up to age 18.[15] They revealed that annual FEV1 and FVC growth

velocities peaked at age 14 in boy, whereas at age 12 in girls, and that impaired lung function progressed into adolescence over time. Respectively, over 50% of CAMP children showed FEV1/FVC below the lower limit of normal lung function (5^{th} percentile).[15] The MAS study showed that asthma or severe asthma in childhood continued to have abnormal lung function and AHR in mid-adult life, on the other hand. Recurrent wheezing at age 7 failed to progression of impaired lung function. Interestingly, ICS was available after 1974 in Australia, therefore none of participants in the MAS cohort used ICS before 18 years of age.[23] This finding supported the finding of CAMP study. It suggested that mild or transient asthma showed no progression of impaired lung function into adolescence, but more severe asthma showed progression of impaired lung function regardless of anti-inflammatory treatment. The MAS study showed that severe asthma had lost lung function by the age of 14 years, and fixed up to age 42.[24] The TCRS study also suggested that AHR and impaired lung function were important risk factors for persistent asthma from childhood into adulthood.[25]

Female gender is known for the risk of adult asthma. The MAS cohort showed female and hay fever were 2 times higher risk of current asthma by age 50.[12] The Isle of Wight (loW) birth cohort showed that transition of allergic sensitization to common allergens, impaired lung function, and smoking were risk factors for the more severe cluster in young adult.[26,27] A few studies have evaluated lung functions in infancy; maximal forced expiratory flow at functional residual capacity (VmaxFRC) by rapid thoracic compression in TCRS[28] and Perth Infant Asthma Follow-up cohort[29]. Lowest quartile of VmaxFRC at infancy was strongly associated with reduced FEV_1, FEV_1/FVC ratio, and FEF_50 in young adult,[28] and higher OR of asthma at age 24 (OR 5.1, 95% CI 2-13).[29]

Relapse

The DMHDS demonstrated that about 30% of those with prior asthma-remission at 18 years of age experienced relapse by age 26, particularly in 60.7% of asymptomatic AHR were relapsed up to age 26.[13]

Adult-onset

The DMHDS cohort showed that smoking was a risk factor for lower FEV_1/FVC ratio in adult-onset asthma.[30] The TCRS reported that 27% of current asthma at 22 years were adult-onset asthma, of which 71% were women, and AHR and impaired lung function at 6 years predicted adult-onset asthma. However, they highlighted that approximately 63% of new-onset asthma at 22 years of age had already reported episodes of wheezing during their childhood.[25] This result highlighted that a considerable numbers of patients did not remember their childhood symptoms. In a pediatrician's view-point, it could be interpreted as not adult-onset asthma, but relapse of childhood one. The British 1958 birth cohort showed that active smoking was related to adult onset of asthma (OR 2.25, 95% CI 1.75-2.89), and continuous smoking at age 16, 23, 33 years showed higher OR of adult onset asthma at age 33 (OR 4.42, 95% CI 3.31-5.92) with

Table 2. Risk factors of asthma persistence or relapse from childhood into adulthood

	Studies	Study design	Sample size	Duration of Follow-up	Results	Definition
Persistence of asthma						
Pneumonia during first three years of life	*TCRS[32]	Non-selective birth cohort Enrolled between 1980-1984	646	Birth to 29 years of age	Asthma; 1.95 (1.11-3.44) Active wheeze; 1.94 (1.28-2.95)	Physician diagnosed pneumonia Physician diagnosed asthma with active symptoms during previous year (attack or wheeze)
Low lung function at birth	*TCRS[28]	Non-selective birth cohort Enrolled between 1980-1984	169	Birth to 22 years of age	Lowest VmaxFRC at infancy showed lower FEV1/FVC ratio (-5.2%), FEV1 (-233 mL) up to age 22	VmaxFRC at 2,3 months of age
	† PIAF cohort[29]	Enrolled between 1987-1990	253	Birth to 24 years of age	Lowest VmaxFRC OR 5.1 (2-13)	VmaxFRC at 1 month of age Questionnaire; physician diagnosed asthma
Severe asthma in childhood	‡ MAS[12]	Enrolled wheezy children at 7 years of age in 1964	484	7 to 50 years of age	Asthma persistence; OR 11.9 (3.4-41.8)	Remission; no wheeze symptoms and no use of asthma medication in the past 3 years, direct telephone interview Wheezy bronchitis; ≥ 5 episodes of wheezing related respiratory infections Asthma; wheezing not associated with respiratory infection Severe asthma; onset < 3 years of age, and > 10 attacks in the 2 years, and FEV_1/FVC ratio < 50%
Relapse of asthma						
Airway hyper-responsiveness	∫ DMHDS[6,13]	Prospective longitudinal studies, not birth cohort	1037	3 to 26	OR 3.0 (1.65-5.55)	Questionnaire based Remission: absence of wheezing at least 2 years Relapse: current wheezing
Sensitization for house dust mite	∫ DMHDS[6,13]	Prospective longitudinal studies, not birth cohort	1037	3 to 26	OR 2.2 (1.18-4.00)	Questionnaire based Remission: absence of wheezing at least 2 years Relapse: current wheezing

*TCRS, Tucson Children's Respiratory Study
† PIAF cohort, Perth Infant Asthma Follow-up cohort
‡ MAS, Melbourne Asthma Study
∫ DMHDS, The Dunedin Multidisciplinary Health and Development Study

dose-dependent response in relation to both duration and amount of active smoking.[9]

As table 2 shows, the risk for adult onset asthma are increased in women, particularly in women with sensitization for the inhalant allergen, allergic comorbidities, active smoking, and pre-existing AHR or

impaired lung function. However, many patients remember a biased recall of their childhood symptoms. Therefore, there is knowledge gap whether adult onset asthma may have originated from early life or not.

The origin of perspectives-gap between pediatric and adult allergist

A substantial knowledge gap exists regarding the transition of asthma from childhood into adulthood. Most of knowledge gap are likely to be caused by different perspectives between pediatric and adult allergist. Childhood studies are lacking of objective measures and information for the endotypes, and heterogeneous definition of asthma. On the other hand, adult studies are lacking of information during childhood.

Conclusion

Most children with early life wheezing may outgrow their symptoms during school years, but asthma relapses are common in young adults. In addition, early impaired lung function may continue to adulthood. Previous studies on the asthma transition from childhood into adult are largely heterogeneous. Remission is common in the mild wheezy infant, but uncommon in children with severe asthma, AHR, or impaired lung function. Some of remitted asthma might persist AHR, impaired lung function, and airway inflammation. Furthermore, some are true adult-onset asthma. However, there is a lack of evidence for where these differences originated. Therefore, I will propose that future research should integrate standardized method, measurement, and molecular approach, and also should be done through collaborative research reflecting common view-point between pediatric and adult allergist.

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