
Relationship between bronchial hyperreactivity and asthma remission during adolescence

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Background: Many children with asthma outgrow this disease after the onset of puberty. However, the precise mechanism of outgrowing asthma in children is still unclear.

Objective: To evaluate the characteristics of respiratory physiology during adolescence.

Methods: The results of the lung function test and methacholine inhalation challenge were prospectively evaluated in adolescent patients with asthma with and without symptoms. One hundred sixty children with asthma participated. Twenty-eight children had symptom-free adolescent asthma (ie, remission asthma) (boy to girl ratio, 16:12; mean age, 14.6 years), 25 had intermittent adolescent asthma (boy to girl ratio, 16:9; mean age, 14.9 years), and 47 had symptomatic adolescent asthma (boy to girl ratio, 27:20; mean age, 12.7 years). For comparison purposes, 60 younger children with symptomatic asthma participated. The parameters of bronchial hyperresponsiveness, baseline respiratory resistance, threshold of methacholine (Dmin) (bronchial sensitivity), and speed of bronchial constriction (Sm) (bronchial reactivity) were measured by methacholine inhalation challenge using the continuous oscillation method.

Results: There was no significant difference in lung function results, such as forced vital capacity and forced expiratory volume in 1 second, between the intermittent asthma and the remission asthma groups. Also, there was no significant difference in baseline respiratory resistance and Dmin between the 2 groups. However, the value of Sm of the remission asthma group was significantly lower than that of the intermittent asthma group ($P = .02$) and the symptomatic asthma group ($P = .02$).

Conclusions: These data show that the adolescents with asthma remission showed a significant decrease of Sm, whereas Dmin was not changed. These results suggest one of the mechanisms by which asthma is outgrown in children and explain the common clinical aspects of adolescent asthma, such as symptom-free but bronchial hyperresponsive asthma.

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INTRODUCTION

Bronchial asthma is among the most common chronic respiratory diseases encountered in the field of pediatrics.¹ An association has been demonstrated between asthma symptoms and bronchial hyperresponsiveness (BHR).² BHR is a consistent and defining feature of asthma, and some reports have suggested that the degree of BHR is more closely related to the severity of asthma than lung function testing results.^{3,4} BHR is already present in infants with asthma and persists for a long time after the diagnosis of asthma.^{5,6}

Many children with asthma outgrow this disease after the onset of puberty.⁷ Recent reports have suggested that BHR disappears at puberty in many individuals, especially girls.⁸ On the other hand, some reports have suggested that the adolescent patients without asthma symptoms still have persistent BHR.⁹ In a clinical study, Wang and coworkers¹⁰ suggested that the relationship between the severity of asthma and BHR in children with asthma shows an age-dependent difference. These data suggest an effect of maturation and/or

aging on the development of BHR. However, the precise mechanism of asthma outgrown in children is still unclear.

The 2 parameters of BHR have been studied by real-time continuous respiratory resistance (Rrs) measurement. The bronchial sensitivity, which is commonly measured by standard methods of histamine or methacholine, suggests how sensitive bronchi react to stimulants. The bronchial reactivity, which is still not a well-known parameter, indicates how quickly the bronchi react. To evaluate the peculiarity of BHR between persistent asthma and remission asthma in adolescents, the differences in lung functions, Rrs, and such BHR parameters in the symptom-free adolescent asthma and symptomatic adolescent asthma groups were studied.

METHODS

Study Protocols

The findings of lung function tests and BHR were prospectively evaluated in adolescents with symptomatic asthma and symptom-free asthma (age range, 10–20 years) who visited the Division of Pediatrics, Gunma University Hospital, Gunma, Japan, between April 1, 2000, and March 31, 2008. All patients were challenged using an oscillation instrument (Astograph, model TCK 6100H; Chest Co, Tokyo, Japan).^{6,11}

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Table 1. The Profiles of Asthmatic Children Within the Age and Asthma Severity Groupings

Age range (mean), y	Total No. (male to female ratio)	Lung function test results, mean (SD)		Baseline Rrs, cm H ₂ O/L per second, mean (SD)
		FVC predicted %	FEV ₁ predicted %	
Children With Symptomatic Asthma				
5–6 (5.8)	37 (20:17)	82.8 (18.0) ^a	71.0 (32.1) ^a	8.53 (1.90) ^a
7–9 (8.0)	33 (19:14)	93.6 (13.1)	85.3 (19.7)	7.09 (1.90) ^a
10–19 (12.7)	48 (27:21)	99.5 (17.8)	87.8 (13.7)	5.59 (1.90)
Children With Intermittent Asthma ^b				
10–19 (14.8)	25 (17:8)	98.5 (15.2)	90.9 (10.8)	5.20 (1.60)
Children With Remission Asthma ^b				
10–19 (14.7)	27 (16:11)	100.8 (16.1)	92.8 (9.1)	4.55 (1.40) ^c

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Rrs, respiratory resistance.

^a $P < .001$ compared with symptomatic asthma in participants aged 10 to 19 years.

^b The average age and the results of lung function testing were similar in the intermittent asthma and the remission asthma groups (by analysis of variance).

^c $P < .05$ compared with symptomatic asthma in participants aged 10 to 19 years.

Participants

This study included 160 children with asthma (96 boys and 64 girls; mean age, 11.3 years). Twenty-eight participants had symptom-free adolescent asthma (16 boys and 12 girls; mean age, 14.6 years), 25 had intermittent adolescent asthma (16 boys and 9 girls; mean age, 14.9 years), and 47 had symptomatic adolescent asthma (27 boys and 20 girls; mean age, 12.7 years). The average age of the adolescents with symptom-free asthma and intermittent asthma was similar (by analysis of variance) (Table 1).

For comparison purposes, 60 young children with symptomatic asthma (age range, 6–9 years; mean age, 7.1 years; 34 boys and 26 girls) participated.

The clinical diagnosis of bronchial asthma was based on a characteristic history of recurrent attacks of dyspnea with perceptible wheezing,^{12,13} and asthma in all patients was diagnosed by physicians. All participants were diagnosed as having atopic asthma because of their reaction to common environmental allergens administered to the skin and the results of radioallergosorbent tests (RASTs) (development of a wheal ≥ 5 mm after a skin prick test and 0.70 Phadebas RAST unit in the RAST was defined as 2+ of reactivity, respectively).

In addition, the number of patients with symptom-free asthma in the adolescent period was small because it was very difficult to obtain informed consent from adolescents who had no medication and less opportunity to undergo medical examinations; the study was, therefore, prolonged for 4 years.

In this study, the participants were classified into 3 groups: (1) participants with symptom-free asthma were defined as the patients who had no asthma attacks and no therapy during the past year or more, (2) participants with intermittent asthma were defined as those requiring only short-term treatment during an asthma attack and those who had fewer than 5 attacks within the past year,¹⁴ and (3) participants with symptomatic asthma were defined as those requiring daily

suitable treatment against asthma and who still had more than 5 series of asthma attacks in a year.

We excluded any participants with severe-persistent asthma, and none of the children were regularly receiving inhaled long-acting β_2 -agonist or oral corticosteroid therapy. All children had been free of respiratory tract infections for more than 4 weeks before enrollment and had received no medication for at least 12 hours before the testing. Approval was obtained from the Gunma University Hospital Ethics Committee, and informed parental consent for each child was obtained before the study.

Methacholine Inhalation Challenge

A methacholine inhalation challenge was performed on all participants, as previously described.¹⁵ Participants underwent the challenge in a seated position, wearing a nose clip. An oscillation instrument was used as the inhalation device and the monitor of real-time Rrs changes. The methacholine inhalation challenge was performed according to the procedure described by Takishima et al.¹⁶ Briefly, the methacholine (Daiichi Kagaku Yakuhin Co, Tokyo) prepared on the day of the test was serially diluted 2-fold with saline (10-dose steps from 25 mg/mL to approximately 49 μ g/mL) and administered via the oscillation instrument. The system consisted of 12 identical nebulizers connected to a main tube and an air compressor that switched from 1 nebulizer to the next at 1-minute intervals. Saline was set up in the first nebulizer as the control. The 12th nebulizer contained salbutamol hemisulfate (1.7 mg/mL in saline) and was administered for 2 minutes.

A constant-amplitude pressure generator was connected to the mouthpiece, and it produced a constant-amplitude pressure of sine waves at the mouth with a loudspeaker box system. A constant bias flow was introduced between the nebulizer and the flow meter to minimize the dead space. The airflow at the mouth was measured with a pneumotachometer

and a differential pressure transducer, which was also used to measure the mouth pressure relative to the ambient pressure. To write the dose-response curves, Rrs was calculated by an analog computer and continuously displayed on the time scale of an X-Y recorder.

The cumulative dose of methacholine at the inflection point at which Rrs increased linearly was taken as the BHR (Dmin) (Fig 1). One Dmin unit was considered to be equal to 1 minute of inhaling an aerosolized methacholine solution (1.0 mg/mL) during tidal breathing. Routine auscultation was performed before and during the methacholine challenges to document wheezing.

Data Analysis

A parametric analysis of variance was performed to determine the significant variance of Dmin between the groups. Data are expressed as mean (SD). The logarithmic values ($\log_{10}$ [mU] of Dmin) were used for the statistical analysis and illustrations. $P < .05$ was considered statistically significant.

RESULTS

In all patients, the inhalation challenge was performed when baseline forced expiratory volume in 1 second (FEV₁) exceeded 70% of the values predicted. During the methacholine inhalation challenge, the maximum decrease of arterial oxygen saturation was between 3 and 6 mm Hg in all patients. All of the children safely underwent the methacholine inhalation challenge without any problem.

Baseline forced vital capacity predicted percentage was 99.5% (17.8%) in the adolescent asthma group, 98.5% (15.2%) in the intermittent asthma group, and 100.8% (16.1%) in the remission asthma group; baseline FEV₁ predicted percentage was 87.8% (13.7%), 90.9% (10.8%), and 92.8% (9.1%) in the 3 groups, respectively. There was no

difference between forced vital capacity and FEV₁ among the 3 groups (Table 1).

The baseline Rrs was significantly decreased with growth, but there was no difference among the intermittent asthma and the remission asthma groups (5.20 [1.60] and 4.55 [1.40] cm H₂O/L per second, respectively), whereas the Rrs of adolescent asthma (5.59 [1.90] cm H₂O/L per second) was higher than that of remission asthma (Table 1).

Among the intermittent asthma and remission asthma groups, there was no difference in Dmin (3.07 [0.70] and 3.27 [0.70] log[mU], respectively) (Fig 2). In contrast, the slope of the methacholine Rrs dose-response curve (Sm) in the remission asthma group (1.29 [0.50] cm H₂O/L per second per minute) was significantly lower than in the adolescent asthma group and the intermittent asthma group (1.73 [0.80] and 1.81 [0.80] cm H₂O/L per second per minute, respectively) (Fig 2).

DISCUSSION

It is well known that adolescents have been observed to outgrow their asthma as they mature.⁷ Previous studies have shown that up to 80% of asthmatic patients lose their symptoms during adolescence.¹⁷⁻¹⁹ In the British national childhood development study, only 5% of symptomatic patients had a persistent wheeze at all times, and more than 50% of the patients who wheezed before the age of 7 years and who reported wheezing in the previous year at the age of 33 years had been free of attacks for 7 years (from the age of 16 to 23 years).²⁰

Such changes in the clinical aspects in asthmatic adolescents are partially due to the dramatic changes in the respiratory system, with structural improvements that occur during this period.²¹ In addition, recent findings suggest that the decline in the prevalence of asthma during the adolescent years may be attributable to the disappearance of the clinical expression of one particular wheezing phenotype primarily associated with viral infections.²²

Although Tantisira et al⁸ have suggested that the concomitant decrease in BHR (airway sensitivity in their report) can explain a real improvement of adolescent asthma, some previous reports have suggested that BHR is persistent in the adolescent period.^{23,24} In a large cohort study of Australian schoolchildren, most children showing a slight or mild degree of BHR lost their increased response at the age of 12 to 14 years, whereas only 15.4% of children with severe or moderate BHR at school age were normoreactive as adolescents.²⁵ In addition, bronchial sensitivity in younger children is closely related to the severity of the asthma, whereas adolescent children aged 14 to 20 years demonstrated no significant relationship between bronchial sensitivity and the severity of asthma.¹⁰ Although little is known about the relationship between BHR and improvement of asthma symptoms, it is important to ascertain how to recognize the outgrowth of childhood asthma because of the strategy for treating asthma in adolescents.

In this report, the main BHR parameters were evaluated by the following technique: bronchial sensitivity and bronchial

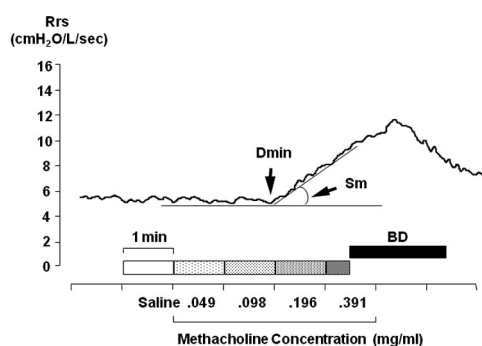


Figure 1. The inflection point of respiratory resistance (Rrs) in methacholine inhalation challenge by the oscillation method. After the inhalation of an incremental challenge of methacholine, Rrs increased. When Rrs reached approximately twice the baseline value, inhalation of methacholine was stopped and, instead, orciprenaline was inhaled. BD indicates bronchodilator inhalation; Dmin, the cumulative dose of methacholine at the inflection point of the Rrs; and Sm, the slope of the methacholine Rrs dose-response curve.

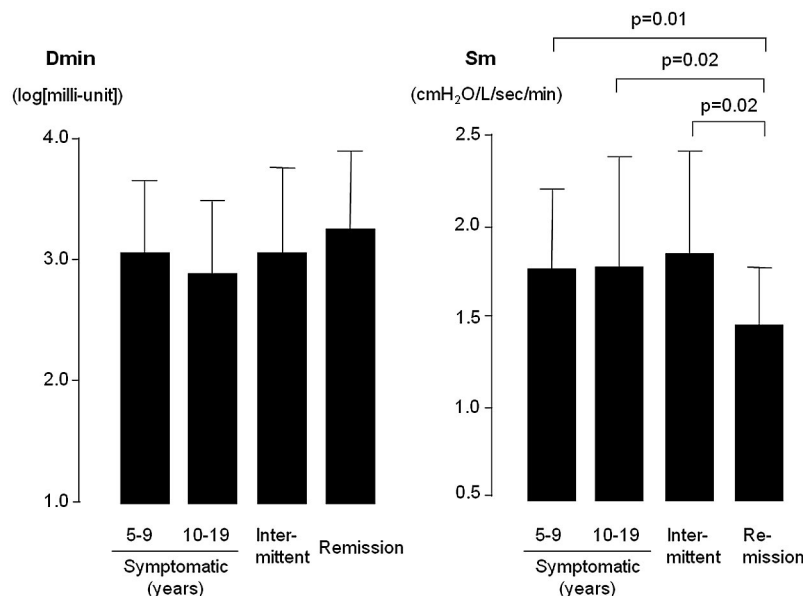


Figure 2. Values for the cumulative dose of methacholine at the inflection point of respiratory resistance (Dmin) and the slope of the methacholine respiratory resistance dose-response curve (Sm) in 4 groups: patients with symptomatic asthma (aged 6–9 and 10–19 years), patients with intermittent asthma, and patients with remission asthma. For Dmin, no significant differences were observed among the 4 groups, and the bronchial sensitivity did not improve even in the remission group. On the other hand, Sm in the remission asthma group was significantly lower than that observed in the other 3 groups, and the speed of airway constriction also decreased in the remission group.

reactivity by real-time continuous Rrs measurement.^{6,11} One key finding of the present study is that not bronchial sensitivity (Dmin) but bronchial reactivity (Sm) statistically decreased in the patients with remission asthma. It is possible that large and quick changes in airway resistance may directly induce apparent respiratory symptoms, such as wheezing and/or dyspnea, but small and slow changes in airway resistance do not induce apparent clinical symptoms.²⁶ The observation that the adolescents with symptom-free asthma show a decrease in bronchial reactivity may thus help to explain the clinical features of adolescent asthma, including the fact that the frequency of respiratory symptoms, such as wheezing and dyspnea, apparently decreases and few problems are found in daily life without medication, except for slight asthma attacks during respiratory infections or after intensive exercise (the laboratory BHR still remains).²⁷

Considering the decrease of Sm in patients with asthma remission, it is possible that increasing airway stability involving airway rigidity induces adolescent asthma improvement. It has been suggested that airway wall rigidity is a potent factor affecting bronchial reactivity in asthmatic patients,²⁸ and the relationship between airway pathophysiological changes and airway rigidity with growth has been reported. Bronchial cartilage hardens with growth, and such hardening may induce airway rigidity. In addition, age-dependent airway remodeling induced by inhaled allergens increases airway rigidity. Although the precise relationship between airway rigidity and human aging is not clear, it is estimated that the hardness of the airways in the patients with

remission asthma is more remarkable than in the patients with intermittent asthma, and the decrease of Sm can be partially affected by the increased stability in the airways, especially in large airways.

Another possibility is that children with remission asthma can introduce increasing airway stability because improved lung function induces an effective delivery of inhaled anti-inflammatory drugs.²³ However, the remission patients in this study had not used inhaled steroids for an extended period before this experiment, and recent reports have suggested that inhaled steroids do not induce persistent improvement of airway inflammation after their discontinued use.^{24,29} In addition, no difference was observed in the lung functions among the remission group, the intermittent group, and the symptomatic asthma group.

On the other hand, there is a strong agreement that the underlying mechanisms of persistent BHR are usually associated with chronic airway inflammation.³⁰ In this report, adolescents with intermittent asthma retain both bronchial sensitivity and bronchial reactivity and, thus, airway inflammation is still present. Considering these results, the remaining bronchial reactivity may therefore help to determine how long anti-inflammatory medication may be required by those patients. However, further study is needed to determine how bronchial reactivity compares with an analysis using the symptoms alone (or traditional spirometry values, such as FEV₁) to appropriately adjust anti-inflammatory treatments.

Consequently, bronchial sensitivity still remains in the adolescents with symptom-free asthma, but bronchial reac-

tivity becomes significantly smaller. The decrease in bronchial reactivity should be used as a gauge of the long-term treatment of asthma, and its disappearance may be a goal for the true remission of asthma during adolescence. However, it has been suggested that few sufficient prospective studies have yet been performed on asthma incidence throughout childhood into early adult life.^{31,32} Adolescence is a very special period in human life, encompassing a wide spectrum of physical and social changes that lead an individual into adulthood. A more detailed study of asthma in adolescence is needed to determine the significance of the remission of childhood asthma in addition to clarifying the important predictors for determining the outcome in adult life.

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