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Phenotypic differences between asymptomatic airway hyperresponsiveness and remission of asthma

Takahiro Yoshikawa [a,*], Hiroshi Kanazawa [b]

[a] Department of Sports Medicine, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan
[b] Department of Respiratory Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

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Asymptomatic airway hyperresponsiveness (AHR);
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Airway narrowing;
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Summary
Background: The present study aimed to illustrate differences in characteristics and perception of dyspnea between young atopic adults who have no history of asthma (*never*-asthmatics) with or without asymptomatic airway hyperresponsiveness (AHR) and those who had childhood asthma and consider themselves to be grown out of the disease (*past*-asthmatics).
Methods: Blood parameters, lung function and methacholine PC_{20} were measured in 88 *never*-asthmatics and 24 *past*-asthmatics. A perception score of dyspnea at 20% fall in FEV_1 (PS_{20}) was obtained by interpolation of the two last points on the perception (modified Borg scale)/fall in FEV_1 curve during methacholine challenge.
Results: Thirty-one of 88 *never*-asthmatics and eighteen of 24 *past*-asthmatics exhibited AHR (PC_{20} was <8 mg/ml). Higher levels of specific IgE to house dust mite in *past*-asthmatics were observed than *never*-asthmatics with and without AHR. Mean values of FEV_1 and FEF_{25-75} (% predicted) were significantly lower in *past*-asthmatics than *never*-asthmatics without AHR, and the values in *never*-asthmatics with AHR were intermediate between *never*-asthmatics without AHR and *past*-asthmatics. PC_{20} was not significantly different between *past*-asthmatics and *never*-asthmatics with AHR. Of particular interest was that PS_{20} was significantly lower in *never*-asthmatics with AHR compared with *past*-asthmatics.
Conclusion: The present findings suggest the possibilities that presence or absence of past history of outgrow of childhood asthma might be associated with airway narrowing, sensitization to house dust mite and perception of dyspnea in young asymptomatic adults with atopy and AHR.

* Correspondence author. Tel.: +81 6 6645 3790; fax: +81 6 6646 6067.
E-mail address: tkhr6719@med.osaka-cu.ac.jp (T. Yoshikawa).

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Introduction

Bronchial asthma is characterized by variable airflow obstruction and airway hyperresponsiveness (AHR). Many studies demonstrated that some of symptom-free individuals, particularly atopic young adults in the absence of a history of pediatric asthma, can also exhibit AHR to various inhaled agents in similar to symptomatic patients with asthma.[1] They usually believe themselves not to have any predisposition related to AHR and asthma. Epidemiological surveys reported that 4–35% of asymptomatic subjects have AHR in general population, even if they had no attacks of wheezing.[2,3] A follow-up study has identified such asymptomatic AHR as one of predictive factors for initiation of future symptomatic asthma.[1]

In a subset of children diagnosed with atopic asthma, respiratory symptoms often remit around puberty.[4,5] Epidemiological studies showed that approximately 50% of adults who reported having asthma in childhood no longer have respiratory symptoms.[4] They often consider themselves to be grown out of their disease at the stage of young adulthood.[6] However, airway narrowing and AHR with mild airway inflammation and structural changes is reported to persist throughout childhood and adulthood even in the absence of respiratory symptoms.[6–12] And respiratory symptoms relapse later in some of these asthmatics.[4,5] Thus, this asymptomatic group is known to be high risk for future onset of asthma, in similar to the asymptomatic AHR described above. However, knowledge is limited regarding similarities and differences in physiological and immunological aspects, including spirometric measures, AHR and allergic sensitization to a specific allergen, between these two asymptomatic subject groups. In addition, it has not been investigated as to differences in perception of dyspnea between these subject groups.

The first objective of the present study was to illustrate differences in spirometric measures, airway responsiveness to inhaled methacholine and allergy sensitization among atopic young adults who were diagnosed with childhood asthma at the school-ages and appeared to have remission of their asthmatic symptoms in adolescence without use of any asthma medication (referred to as *past*-asthmatics) and age-matched atopic adults who do not have any past history of wheeze symptoms (referred to as *never*-asthmatics) with or without asymptomatic AHR. Second, the present study aimed to examine the difference in perception of dyspnea for bronchoconstriction after methacholine inhalation among these subject groups. We hypothesized that the spirometric variables, atopic parameters in blood and perception of dyspnea by bronchoconstriction in *never*-asthmatics with AHR might differ from those in age-matched *never*-asthmatics without AHR and *past*-asthmatics. Examination of such differences might help us to characterize *never*-asthmatics with AHR and *past*-asthmatics and to delineate the natural history of AHR and asthma at the time of young adulthood.

Methods

Subjects were first recruited at random on the basis of a list of university students and only never-smokers were asked to participate in the present study, including the blood sampling and methacholine provocation testing. A clinical history was taken and physical examination was performed on all volunteers who agreed with the participation. Blood samples were also collected from the same volunteers. Then, only those who met at least one of the following criteria were finally included in the present study; 1) current or past history of allergic diseases, such as hay fever and atopic dermatitis diagnosed by specialists, 2) a total serum IgE level of more than 250 IU/ml, or 3) one or more specific IgE levels of more than 0.34 Ua/ml to house dust mite (*Dermatophagoides pteronyssinus*), cat dander, dog dander, or cedar pollen as determined by radioallergosorbent test (RAST) using UniCAP IgE fluoroenzyme-immunoassays (Sweden Diagnostics, Uppsala, Sweden).

Then, the study subjects were divided into two categories based on self-reported information; 1) those who do not have any past history of wheeze symptoms (*never*-asthmatics) and 2) those who had a history of asthma at their school-ages diagnosed by pediatric specialists but had no wheeze symptoms without use of any asthma medication for at least 3 preceding years (*past*-asthmatics).[13] Furthermore, *never*-asthmatics were divided into two groups according to the airway response to methacholine exposure; those with or without AHR.

A spirometer (Chestac-25F; Chest CO., Tokyo, Japan) was used to obtain all spirometric measurements (FEV_1, FVC, FEV_1/FVC and FEF_{25-75}). The methacholine provocation test was performed for all subjects as recommended by American thoracic Society (ATS) guidelines.[14] Briefly, subjects inhaled saline (baseline) or methacholine solution (0.3–16 mg/ml) for 2 min by tidal breathing from a Devilbiss 646 nebulizer (Devilbiss Co., Somerset, PA, USA) operated with compressed air at 5 l/min. Spirometry was performed about 30 s after inhalation and FEV_1 was measured. The measured values were plotted on a semi-logarithmic graph and the provocative concentration of methacholine causing a 20% fall in the FEV_1 (PC_{20}) was calculated in noncumulative units by linear interpolation between the last two points on the graph. If there was a $>$20% fall in FEV_1 to a methacholine concentration (PC_{20}) $<$8 mg/ml, the subject was categorized as having AHR. In addition, immediately before each FEV_1 measurement during the methacholine challenge, perception of dyspnea were evaluated according to a modified Borg scale from 0 (no symptom) to 10 (maximal bearable).[15] Scores between the fixed intervals were permitted (half an interval, 0.5). A perception score at a 20% fall in FEV_1 (PS_{20}) was obtained by interpolation of the two last points on the perception/fall in FEV_1 curve according to previous studies.[16,17] The PS_{20} was calculated only in the group of *never*-asthmatics with asymptomatic AHR and that of *past*-asthmatics who exhibited a significant fall (20%) in FEV_1 because the PS_{20} values cannot be estimated by interpolation unless more than 20% fall in FEV_1 is produced by the methacholine inhalation.

All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL). Results are expressed as median (range). Spirometric data, which were normally distributed, are presented as mean $\pm$ SD. Age, blood eosinophils, serum IgE levels (specific to four common allergens described above) and methacholine PC_{20} for three volunteer