Characteristics of Young Atopic Adults with Self-Reported Past Wheeze and Airway Hyperresponsiveness

Takahiro Yoshikawa1 and Hiroshi Kanazawa2

ABSTRACT

Background: The present study aimed to illustrate clinical characteristics of spirometric measures and allergy sensitisation among young atopic adults who reported wheezing episodes before adulthood but were not diagnosed with asthma by physicians and have no current wheeze symptoms (self-reported past-wheezers), especially those who exhibited airway hyperresponsiveness (AHR).

Methods: Fifty self-reported past-wheezers were divided into two groups according to AHR to methacholine. Spirometric functions and blood atopic parameters were compared in these groups with those in 25 age-matched atopic adults with a history of childhood asthma diagnosed by specialists but have no current wheeze symptoms (past-asthmatics) and in 60 counterparts without a previous and current wheezing episode (never-wheezers).

Results: Twenty-one of the 50 past-wheezers exhibited AHR (PC20 <8 mg/ml). Levels of spirometric function and allergic sensitization in both past-wheezers groups were intermediate between those in never-wheezers and past-asthmatics. Lower FEV1 and FEF25-75 values (% predicted) were observed in self-reported past-wheezers relative to those without AHR. More blood eosinophils and higher serum levels of total IgE and IgE specific to house dust mites were observed in self-reported past-wheezers with AHR relative to those without AHR.

Conclusions: Our findings raise the possibility that self-reported past-wheezers with AHR might form a distinct subgroup with features similar to past-asthmatics, which is one of the risk groups for adult asthma.

KEY WORDS

airway hyperresponsiveness (AHR), asthma, house dust mites, lung-function tests, wheeze

INTRODUCTION

Asthma is a clinical syndrome that is generally diagnosed according to a history of respiratory symptoms and objective measurements of lung function and airway inflammation. In particular, wheezing is a characteristic symptom that is used for diagnosis, along with coughing and chest tightness. However, the nature of wheezing disorders varies among individuals, particularly during childhood. Early-life wheezing illness among preschool children can be characterised into distinct subtypes (transient early, late-onset or persistent) based on the symptom history. Furthermore, such wheezing types early in life are thought to determine the expression of asthma and the level of lung function later in life. Similarly, wheezing symptoms may emerge during adolescence, even in atopic individuals who did not experience any wheezing episodes during preschool, and the lung growth (assessed by FEV1) is known to be reduced. These

1Department of Sports Medicine and 2Department of Respiratory Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan.

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Correspondence: Takahiro Yoshikawa, Department of Sports Medicine, Osaka City University Graduate School of Medicine, 1–4–3 Asahi-machi, Abeno-ku, Osaka 545–8585, Japan.

Email: tkhr6719@med.osaka–cu.ac.jp

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A subset of young atopic adults without current respiratory symptoms present with a history of wheezing from early infancy through adolescence but were not diagnosed with asthma by a physician (referred to as self-reported past-wheezers). They often attribute their previous wheezing symptoms to a bad cold. In contrast, almost half of young atopic adults previously diagnosed with childhood asthma no longer have respiratory symptoms (referred to as past-asthmatics). They often consider themselves to be grown out of their disease at the stage of young adulthood. Despite the remission of symptoms, however, these past-asthmatics are known to have occult impairment in pulmonary function, such as that assessed by FEV1 and FEF25-75, and higher levels of specific IgE to house dust mite in past-asthmatics were observed than in young atopic adults who have no history of asthma. Until now, the similarities and differences in spirometric measures and allergy sensitisation among self-reported past-wheezers, past-asthmatics and age-matched young atopic adults with no history of wheezing (referred to as never-wheezers) have not been fully described. Furthermore, it is also unknown whether the physiological and serological characteristics of self-reported past-wheezers are related to the presence or absence of airway hyperresponsiveness (AHR). Previous longitudinal studies have demonstrated that, in children and young adults who have had ‘recent’ wheezing episodes within the previous 12 months, the coexistence of AHR represents a clinically relevant disease entity that is associated with asthma, including lower lung function.

The objective of the present study was to compare spirometric measures and allergy sensitisation in young atopic adult self-reported past-wheezers with or without AHR, to those in past-asthmatics and age-matched atopic never-wheezers. Examining these differences might help us characterise young atopic adult self-reported past-wheezers, evaluate the importance of identifying self-reported past-wheezers in clinical settings, and delineate a part of the natural history of asthma-related wheezing phenotypes at the stage of young adulthood.

METHODS
Subjects were recruited randomly from a list of uni-
Table 1 Characteristics of all subjects

<table>
<thead>
<tr>
<th>Subjects without past history of wheeze (Never-wheezees) (n = 60)</th>
<th>Subjects with past history of wheeze (Self-reported past-wheezees) without AHR (PC20 ≥8 mg/mL) (n = 29)</th>
<th>Subjects with past history of wheeze (Self-reported past-wheezees) with AHR (PC20 &lt;8 mg/mL) (n = 21)</th>
<th>Subjects with remission of asthma (Past-asthmatics) (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>19 (18-20)</td>
<td>19 (18-20)</td>
<td>19 (18-20)</td>
<td>19 (19-20)</td>
</tr>
<tr>
<td>Sex [M/F]</td>
<td>19/41</td>
<td>14/15</td>
<td>8/13</td>
<td>7/18</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>20.7 (19.6-22.1)</td>
<td>20.8 (19.5-21.8)</td>
<td>21.0 (19.7-21.7)</td>
<td>20.2 (18.7-20.9)</td>
</tr>
<tr>
<td>Allergic Rhinitis [%]</td>
<td>56.7</td>
<td>62.1</td>
<td>71.4</td>
<td>76.0</td>
</tr>
<tr>
<td>Atopic dermatitis [%]</td>
<td>22.9</td>
<td>14.3</td>
<td>25.0</td>
<td>21.1</td>
</tr>
</tbody>
</table>

Age and BMI were not normally distributed and presented as median (25 and 75 percentile). These values for the volunteer groups were compared by Kruskal-Wallis one-way analysis of variance on ranks. Categorical data for the volunteer groups were compared by chi-square test. No significant differences among the subject groups were observed in these parameters. During methacholine testing, subjects inhaled saline (baseline) or methacholine solution (0.3-16 mg/mL) for 2 min by tidal breathing. Of the 50 self-reported past-wheezees, 21 (42.0%) exhibited significant AHR (PC20 ≥2.3 mg/mL). 25th to 75th percentile; median 3.6 mg/mL. All subjects (n = 135) are life-long non-smokers. BMI, body mass index; AHR, airway hyperresponsiveness.

A spirometer (Chestac-25F; Chest Co., Tokyo, Japan) was used to obtain all of the spirometric measurements (FEV1, FVC, FEV1/FVC and FEF25-75). For all of the self-reported past-wheezees, the methacholine provocation test was performed as recommended by the American Thoracic Society (ATS) guidelines. Briefly, the subjects inhaled saline (baseline) or methacholine solution (0.3-16 mg/mL) for 2 min by tidal breathing from a Devilbiss 646 nebuliser (Devilbiss Co., Somerset, PA, USA). Spirometry was performed approximately 30 seconds after each inhalation, and the FEV1 was measured. These measured values were plotted on a semilogarithmic graph, and the concentration of methacholine that was able to provoke a 20% drop in FEV1 was calculated in noncumulative units by linear interpolation between the last two points on the graph. If the PC20 was <8 mg/mL, the subject was categorised as having AHR. All visits were conducted outside the pollen season in subjects with seasonal allergic symptoms.

All of the statistical analyses were performed using SPSS ver.18 for Windows (SPSS Inc., Chicago, IL, USA). Results are expressed as medians (25th and 75th percentiles). However, the spirometric data, which were normally distributed, are presented as mean ± SD. Serum total IgE levels were transferred to a logarithmic function to yield normally skewed data during the analyses. The age, BMI, blood eosinophils and serum specific IgE levels of subject groups were compared using the nonparametric Kruskal-Wallis test. The Mann-Whitney U-test was performed for comparison between two subject groups after the Kruskal-Wallis test when appropriate. The spirometric data and the log values of serum total IgE of sub-
Mean values of FEV₁ (% predicted), obtained from never-wheezers, self-reported past-wheezers both without AHR and with AHR and past-asthmatics in young atopic adults who are currently asymptomatic. These spirometric parameters were significantly lower in the past-asthmatics than in never-wheezers and self-reported past-wheezers without AHR. And the self-reported past-wheezers with AHR had reduced spirometric function compared with those without AHR. Never-wheezers, subjects with no past history of wheezing symptoms; Self-reported past-wheezers, subjects with a childhood/adolescent history of wheezing symptoms but without an asthma diagnosis; Past-asthmatics, subjects 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; AHR, airway hyperresponsiveness.
Fig. 3  Blood eosinophil counts (per mm$^3$) obtained from never-wheezers, self-reported past-wheezers both without AHR and with AHR and past-asthmatics in young atopic adults who are currently asymptomatic. The horizontal bars represent the median values for each subject group. Higher eosinophil counts were observed in past-asthmatics than in never-wheezers and self-reported past-wheezers without AHR. Similarly, the self-reported past-wheezers with AHR had increased numbers of eosinophils compared with those without AHR and never-wheezers. Never-wheezers, subjects with no past history of wheezing symptoms; Self-reported past-wheezers, subjects with a childhood/adolescent history of wheezing symptoms but without an asthma diagnosis; Past-asthmatics, subjects 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; AHR, airway hyperresponsiveness.

**RESULTS**

Sixty never-wheezers (19 males, 41 females; aged 18 to 20 yrs), 50 self-reported past-wheezers (22 males, 28 females; aged 18 to 20 yrs) and 25 past-asthmatics (7 males, 18 females; aged 19 to 20 yrs) participated in the study (Fig. 1). Table 1 presents the background information on the subjects. No significant differences were observed among four subject groups in BMI, prevalence of allergic rhinitis and atopic dermatitis. Of the 50 self-reported past-wheezers, 21 (42.0%) exhibited significant AHR (PC$\text{20}$ 2.3 to 5.0 mg/mL (25th to 75th percentile); median 3.6 mg/mL).

The mean baseline FEV$_1$ and FEF$_{25-75}$ (% predicted) values were lower in past-asthmatics compared with never-wheezers and self-reported past-wheezers without AHR (FEV$_1$; $P = 0.003$ by one-way ANOVA, $P = 0.020$ vs. never-wheezers and $P < 0.001$ vs. self-reported past-wheezers without AHR by *post-hoc* test, FEF$_{25-75}$; $P = 0.027$ by one-way ANOVA, $P = 0.029$ vs. never-wheezers and $P = 0.004$ vs. self-reported past-wheezers without AHR by *post-hoc* test, respectively) (Fig. 2A, 2B). In addition, these spirometric parameters were lower in self-reported past-wheezers with AHR compared with those without AHR (FEV$_1$, $P = 0.025$; FEF$_{25-75}$, $P = 0.05$ by *post-hoc* test). The FVC and FEV$_1$/FVC values were not significantly different among the subject groups (data not shown).

The blood eosinophil counts were significantly higher in past-asthmatics compared with never-
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**Fig. 4** Mean values of total serum IgE levels obtained from never-wheezers, self-reported past-wheezers both without AHR and with AHR and past-asthmatics in young atopic adults who are currently asymptomatic. The serum levels were transferred to a logarithmic function to produce normally skewed data. Higher total IgE levels in serum were observed in the self-reported past-wheezers with AHR compared with those without AHR. Never-wheezers, subjects with no past history of wheezing symptoms; Self-reported past-wheezers, subjects with a childhood/adolescent history of wheezing symptoms but without an asthma diagnosis; Past-asthmatics, subjects 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; AHR, airway hyperresponsiveness; IgE, immunoglobulin E.

Wheezers and self-reported past-wheezers without AHR ($P = 0.027$ by Kruskal-Wallis test, $P = 0.033$ vs. never-wheezers and $P = 0.027$ vs. self-reported past-wheezers without AHR by Mann-Whitney U-test) (Fig. 3). Significant higher counts of eosinophils were also observed in self-reported past-wheezers with AHR compared with those without AHR and never-wheezers ($P = 0.025$ vs. self-reported past-wheezers without AHR and $P = 0.043$ vs. never-wheezers by Mann-Whitney U-test). All participants had above-normal serum total IgE or specific IgE levels. While the mean level of serum total IgE in past-asthmatics was not significantly different from other subject groups, higher levels were observed in the self-reported past-wheezers with AHR compared with those without AHR ($P = 0.048$ by one-way ANOVA, $P = 0.017$ by *post-hoc* test) (Fig. 4). In particular, the levels of IgE specific to house dust mites was significantly higher in past-asthmatics than in self-reported past-wheezers without AHR and never-wheezers ($P = 0.015$ by Kruskal-Wallis test, $P = 0.009$ vs. self-reported past-wheezers without AHR and $P = 0.020$ vs. never-wheezers by Mann-Whitney U-test) (Fig. 5).

Higher median value was observed in self-reported past-wheezers with AHR compared with those without AHR ($P = 0.044$ by Mann-Whitney U-test).

**DISCUSSION**

In the present study, we sought to identify the clinical characteristics of young atopic adult self-reported past-wheezers, particularly those with AHR, by comparison to those of never-wheezers and past-asthmatics. Reduced spirometric values and increased atopic blood parameters were found in past-asthmatics compared with the age-matched never-wheezers and self-reported past-wheezers without AHR. Similarly, self-reported past-wheezers with AHR had lower spirometric function levels and higher allergen sensitisation levels than those without AHR.

To date, many prospective studies have documented the time course and outcomes of wheezing disorders and revealed that they are highly variable. In particular, some of children with wheezing disorders are at risk for impaired lung function growth; subsequently at an increased risk for developing asthma, even if the clinical symptoms subside.
in adolescence. In the present study, we first highlighted a group of the self-reported past-wheezers in atopic young adulthood. We hypothesized that the clinical features of the population might be intermediate and diverse between never-wheezers and past-asthmatics. In fact, the present study demonstrated that, while spirometric values and blood atopic parameters did not differ between past-wheezers without AHR and never-wheezers, those with AHR had reduced FEV1 and FEF25-75 values (% predicted) and increased levels of eosinophils, total IgE and IgE specific for house dust mites in the blood similar to those of past-asthmatics. This observation raises the possibility that the past-wheezers with AHR might form a distinct subgroup with clinical implications of a possible risk factor for adult asthma. Accordingly, the evidence indicates that attention needs to be paid to the self-reported past-wheezers, in particular those with AHR, and raises the issue about definition of whom we should monitor and treat in such intermediate group.

Although numerous articles have so far debated the best way to define and classify the disease of asthma and wheezing disorders for epidemiological purposes, these works reveal an uncertainty about the exact features that identify subjects with a clinically important disease rather than respiratory symptoms without important sequelae. First, such uncertainty is especially true given that patients have one or only a few of clinical features of asthma transiently. For example, previous studies showed that wheezing symptom alone does not necessarily correlate with the presence of other asthma characteristics in children; this symptom might also be caused by a transient airway narrowing or closure resulting from inflammation (i.e., following a viral infection), or it might occur spontaneously as a result of the individual airway structure, particularly in preschool children. Second, it appears that this uncertainty might also arise from a lack of understanding of the com-

**Fig. 5** Serum levels of IgE specific to house dust mites obtained from never-wheezers, self-reported past-wheezers both without AHR and with AHR and past-asthmatics in young atopic adults who are currently asymptomatic. The horizontal bars represent the median values for each subject group. Higher levels of the specific IgE were observed in the past-asthmatics compared with the levels observed in never-wheezers and self-reported past-wheezers without AHR. And the self-reported past-wheezers with AHR had increased levels of the specific IgE compared with those without AHR. Never-wheezers, subjects with no past history of wheezing symptoms; Self-reported past-wheezers, subjects with a childhood/adolescent history of wheezing symptoms but without an asthma diagnosis; Past-asthmatics, subjects 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; AHR, airway hyperresponsiveness; IgE, immunoglobulin E.
plex relationships among subjective symptoms and objective parameters that represent the presence of asthma. For example, while the wheezing symptoms and reduced spirometric function can be observed in the absence of AHR in early life, AHR can develop even in the absence of symptoms. Previous longitudinal studies have indicated a negative impact of ‘recent’ wheezing episodes and concomitant AHR on subsequent FEV1 increases that were observed from age 8 to 19. In this sense, the present findings add new evidence because not only ‘recent’ but also a past history of wheezing episodes in the presence of AHR could indicate a specific asthma-related phenotype in currently asymptomatic young adults with atopy.

Latent airway inflammation and structural remodeling underlying persistent spirometric abnormalities were known to be observed in past-asthmatics. Likewise, it is assumed that such pathophysiological changes might also develop in the airways of the self-reported past-wheezers with AHR, given their observed clinical similarity to the past-asthmatics. Higher levels of blood eosinophils and IgE specific to house dust mites in the past-wheezers might indicate the presence of such airway changes, though not directly assessed. Future investigations to illuminate the pathophysiological determinants of the development of self-reported wheezing with AHR by direct assessment of airway biomarkers might provide a better picture of the natural history of asthma, wheezing disorders and AHR.

There are some potential limitations to the present findings. First, recall bias could possibly have no small effect on the participant responses to interview questions about the presence or absence of past wheezing episodes per se in the present study. Second, the study could not fully reveal alone whether the phenotype (with AHR) really constitutes a risk factor of future onset of asthma because the self-reported past-wheezers with or without AHR were not prospectively evaluated in the present study. Thus, prospective studies will also be needed to examine the risk of adult-onset asthma, the rate of decline in spirometric function and the change in prevalence and severity of AHR in young adult self-reported past-wheezers with AHR compared with age-matched counterpart with a childhood history of asthma. However, the present study at least demonstrated that self-reported past-wheezers with AHR exhibited reduced spirometric function during asymptomatic young adulthood and that, if the disease appears later, it impacts these individuals severely (with lower pulmonary function evident even at the initial stage of the disease).

In summary, the present findings reveal evidence that the population of self-reported past-wheezers might include various clinical entities and underscore the significance of this population in that a past history of wheezing symptoms in childhood and adolescence are useful for clinically categorising young adult individuals with asthma-related conditions. To characterise the intermediate clinical conditions, which lie on the broad continuum between complete health and severe disease in terms of asthma-related conditions, such undiagnosed self-reported wheezing symptoms might provide useful information for defining asthma and understanding the natural history of asthma-related subtypes.

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