INTERNAL MEDICINE

A History of Ischemic Heart Disease is a Common Cause of Wheezing in the Elderly of a Japanese Local Community

Minehiko Inomata[1], Yukio Kawagishi[1,2], Kotaro Tokui[1], Yasuaki Masaki[1], Chihiro Taka[1], Kenta Kambara[1], Seisuke Okazawa[1], Shingo Imanishi[1], Tomomi Ichikawa[1], Kensuke Suzuki[1], Toru Yamada[1], Minoru Iwata[1], Isao Usui[1], Shigeki Sumi[3,4], Hideki Origasa[4], Shoko Matsui[5], Ryuji Hayashi[1] and Kazuyuki Tobe[1]

Abstract

Objective   We conducted a cross-sectional study to investigate which factors have a significant impact on wheezing and QOL in the elderly of a Japanese local community.

Methods   In 2008, 527 participants (250 participants aged 45 to 64 years and 277 participants aged 65 to 88 years) responded to the questionnaire regarding wheezing and disease history. QOL was evaluated by the Short Form-8. The participants underwent airway reversibility testing. The plasma levels of IgE were measured. The plasma levels of N-terminal-pro-B-type natriuretic peptide were measured in twenty-one participants with a history of ischemic heart disease and in thirty-five age-matched participants without that history.

Results   Wheezing was reported by 50 (9.5%) participants and was associated with a lower score of QOL. In multivariate analysis, wheezing was associated with sex (OR 3.12, CI 1.10-9.67) and a history of bronchial asthma (OR 22.3, CI 6.50-84.0) among participants aged 45 to 64 years. Among participants aged 65 and over, wheezing was associated with a history of bronchial asthma (OR 4.86, CI 1.39-15.1) and ischemic heart disease (OR 5.12, CI 1.61-15.0). Participants with both a history of ischemic heart disease and wheezing showed higher levels of N-terminal-pro-B-type natriuretic peptide. Airway reversibility was only associated with a history of ischemic heart disease (OR 4.65, CI 1.26-17.6).

Conclusion   It is suggested that bronchial asthma and heart disease are both significant causes of wheezing and affect the QOL in the elderly of a Japanese local community.

Introduction

Asthma is a common disease and the number of asthmatic patients is estimated about 300 million and still increasing all over the world (1). Recently, therapeutic advances in asthma management, such as the use of inhaled corticosteroids, have not only resulted in improvement in the asthma symptoms in most patients, but also brought about a decrease in asthma deaths (2, 3). However, asthma in the elderly (65 years or over) is more problematic because of its diagnostic issues and mortality (4, 5).

Wheezing is a primary symptom of bronchial asthma and is the most sensitive question for asthma survey (6). However, most studies showed that the prevalence of wheezing was almost twice or more than that of defined asthma (6, 7). Recently, a Japanese nationwide study, in which we participated, revealed the asthmatic and wheezing prevalence in Japan (8). That study also showed that the prevalence of wheezing was almost twice that of asthmatics. However, the

causes of wheezing other than asthma have rarely been studied in a population-based study.

Asthma-related symptoms such as wheezing are significantly associated with the quality of life (QOL) (9). Therefore, the precise diagnosis of wheezing and proper treatment of individuals with wheezing is important for the affected people.

Wheezing in the elderly may be the manifestation of various diseases other than asthma, such as chronic obstructive pulmonary disease (COPD), congestive heart failure, pulmonary aspiration, and lung cancer (10). COPD is one of the most frequent causes of respiratory illness in the elderly and its symptoms resemble asthma (11). Another important disease that manifests similar symptoms as asthma is heart disease (12). Because heart disease is also prevalent in the elderly, it is more difficult to conduct an asthma survey based on asthmatic symptoms.

It is important to elucidate wheezing prevalence and the causes of wheezing in elderly individuals because the aging society is growing and wheezing itself can be a cause of decreased QOL. The aim of this cross-sectional study was to evaluate the prevalence of wheezing and the association between wheezing and QOL, and to elucidate the etiology of wheezing in the elderly population aged 65 years or over compared with a middle-aged population aged 45 to 64 years in a Japanese local community.

Materials and Methods

The subjects of investigation

This study was performed in Jinbo, a town of Toyama city with a population of 5,007 including 2,465 people aged 45 years old or over. All of the subjects aged 45 years old or over were invited to participate in the study at regional community centers and 527 of them (21.4%) responded to the invitation and completed the questionnaire. We divided participants into two categories according to age: 45 to 64, middle aged (n=250), and 65 to 88, elderly (n=277). The study was conducted with the approval of the Ethics Committee of the University of Toyama (Ethics Committee, University of Toyama), and all participants were assured that their personal health information would be kept confidential and secure.

Questionnaire

We asked the participants to complete the questionnaire regarding wheezing, smoking status, and a history of bronchial asthma, ischemic heart disease, and allergic rhinitis. Wheezing was assessed by asking "Have you had wheezing or whistling in your chest at any time in the last twelve months?"

QOL was evaluated by the Short Form-8 (SF-8). The SF-8 is an abbreviated form of the Short Form-36 that is used for large-scale health measurements (13). The physical component summary (PCS) and mental component summary (MCS) scores were calculated; higher scores indicated a higher-quality health status.

Lung function test

Spirometry was completed as recommended by the American Thoracic Society/European Respiratory Society (14). All participants underwent baseline lung function testing and repeated the required maneuvers three times while wearing nose clips. The highest of the three measured FEV_1 values was used for the analysis. Salbutamol was administered by inhalation through a spacer device at a dose of 200 μg, and the test was repeated 30 minutes later. Subjects who were 86 years or older, had hyperthyroidism, extraordinary hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg), tachycardia, active angina pectoris, active congestive heart failure, anxiety and were considered not to be appropriate for salbutamol inhalation, as assessed by examining doctors, were excluded from the bronchodilator test. Seventy of the 527 subjects (13.3%) were excluded by the exclusion criteria. Therefore, 457 subjects underwent the bronchodilator test. An increase in the FEV_1 by 12% of baseline and 0.2L was considered to represent significant airway reversibility. Participants with an FEV_1/FVC ratio <0.7 were diagnosed with airflow limitation.

IgE and NT-pro-BNP measurement

The plasma levels of total non-specific IgE and allergen-specific IgE (measured by a radioallergosorbent test, or RAST) were measured for all participants. The plasma level of creatinine and N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) levels in participants with a history of ischemic heart disease (n=21) and in some of the participants with no history of ischemic heart disease (n=35) were measured.

Statistical analysis

Data are presented as the mean (SD) unless otherwise indicated. Analyses were performed using a statistical software package (JMP, version 9.0.0). Fisher's exact test was used to compare categorical variables, and Student's t test and Wilcoxon's rank sum test were used to compare numerical variables. Multiple regression analyses were used to assess the association between the QOL scores, lung function, and wheezing. A logistic regression analysis was used to identify the independent risk factors for wheezing and airway reversibility in the middle-aged and elderly participants. The plasma levels of NT-pro-BNP in groups were compared by analysis of variance (ANOVA) followed by a Tukey's test. A p value of <0.05 was considered to be statistically significant.

Results

Table 1 shows participant characteristics. The survey questionnaire was completed by 527 participants. The mean

Table 1. Demographic Characteristics and Disease History According to Age

Age	Whole	45-64	65-88	p
Number of participants	527	250	277	
Men	219 (41.6%)	98 (39.2%)	121 (43.7%)	0.33
Smoking history	156 (29.6%)	94 (37.6%)	62 (22.4%)	0.0002
History of bronchial asthma	31 (5.9%)	15 (6.0%)	16 (5.8%)	1.00
History of allergic rhinitis	120 (22.8%)	74 (29.6%)	46 (16.6%)	0.0004
History of ischemic heart disease	21 (4.0%)	2 (0.8%)	19 (6.9%)	0.0002
Wheezing	50 (9.5%)	21 (8.4%)	29 (10.5%)	0.46

Table 2. Results of Baseline Lung Function Testing, Airway Reversibility Testing, and IgE Measurements

Age	Whole	45-64	65-88	p
Number of participants	527	250	277	
Base line FEV_1% pred.	96.5(22.0)	95.9(21.4)	97.1(22.5)	0.53
Post-bronchodilator FEV_1% pred. [*]	105.0(20.0)	104.0(18.6)	105.8(21.2)	0.34
base line airflow limitation	63 (12.0%)	21 (8.4%)	42 (15.2%)	0.022
Post-bronchodilator airflow limitation[*]	44 (9.6%)	18 (8.1%)	26 (11.1%)	0.34
Airway reversibility[*]	89 (19.5%)	38 (17.0%)	51 (21.8%)	0.24
Total IgE (IU/mL) [†]	55 (21-168)	63 (21.8-198.3)	48 (20-159)	0.22
Cedar pollen[§]	113 (21.4%)	81 (32.4%)	32 (11.6%)	<0.0001
House dust[§]	76 (14.4%)	50 (20.0%)	26 (9.4%)	0.0007

* Data of participants who underwent reversibility testing (n = 457).
† Values represent median (interquartile range).
§ Number of participants with allergen-specific IgE (positive rate).

age of all participants was 64.9 (SD 9.5, range 45 to 88 years old) and 41.6% of them was men. We divided participants into two categories according to age: 45 to 64, middle aged, and 65 to 88, elderly. We compared the wheezing prevalence and other associated factors of the two groups. Histories of ischemic heart disease were reported more frequently in participants aged 65 to 88 years, and histories of allergic rhinitis were reported more frequently in participants aged 45 to 64 years. Wheezing was reported in fifty (9.5%) participants and we found no significant difference of frequency of wheezing between each group.

Table 2 shows lung function testing and IgE measurement results. Sixty three (12.0% of whole participants) participants showed pre-bronchodilator airflow limitation. Airway reversibility testing was completed in 457 participants. The mean change of FEV_1 after inhalation of the bronchodilator (ΔFEV_1) was 97.2 mL, and its relative change was 5.4%. Eighty-nine (19.5% of participants who underwent reversi-

bility testing) participants showed airway reversibility and forty-four participants (9.6% of participants who underwent reversibility testing) showed post-bronchodilator airflow limitation. Allergen-specific IgE was detected more frequently in the younger participant group.

Table 3 shows the association between wheezing or lung functions and SF-8 scores. Participants with wheezing showed significantly lower PCS scores after adjusting for age, sex, and past histories. However, airflow limitation and airway reversibility were not associated with the QOL score.

In the participants aged 45 to 64 years, sex (men, OR 3.45, 95%CI 1.34-8.89, p=0.0096), a history of bronchial asthma (OR 27.88, 95% CI 8.52-91.18, p<0.0001), and allergic rhinitis (OR 2.90, 95% CI 1.17-7.16, p=0.024) were identified as being significantly associated with wheezing in the univariate analysis. However, other factors such as airway reversibility (OR 0.52, 95% CI 0.11-2.32, p=0.54), pre-(OR 1.16, 95% CI 0.25-5.38, p=0.69) or post-bronchodilator

Table 3. Association between SF-8 Scores and Wheezing or Lung Function

		PCS	p	MCS	p
Wheezing	(+) n=50	45.9(6.8)	0.027	48.2(6.8)	0.090
	(-) n=477	48.5(6.0)		50.3(5.5)	
Airway reversibility	(+) n=89	48.0(6.9)	0.56	50.2(5.6)	0.63
	(-) n=368	48.7(5.7)		50.2(5.8)	
Pre-bronchodilator airflow limitation	(+) n=63	46.6(7.1)	0.16	49.0(5.7)	0.16
	(-) n=464	48.4(5.9)		48.5(6.0)	
Post-bronchodilator airflow limitation	(+) n=44	49.0(6.6)	0.28	49.5(7.3)	0.34
	(-) n=413	50.3(5.5)		50.3(5.5)	

Definition of abbreviations: PCS = physical component summary; MCS = mental component summary
p values were calculated after adjusting for age, sex, and past history of asthma, allergic rhinitis, and ischemic heart disease.

Table 4. Multivariate Analyses to Assess the Relationship between Wheezing and a History of Diseases among According to Age

45 to 64 years (n=250)				65 to 88 years (n=277)			
Variables	OR	95% CI	p	Variables	OR	95% CI	p
Age	1.08	0.97-1.21	0.17	Age	1.00	0.92-1.07	0.92
Men	3.12	1.10-9.67	0.033	Men	0.88	0.38-1.97	0.75
Bronchial asthma	22.32	6.50-84.0	<0.0001	Bronchial asthma	4.86	1.39-15.1	0.015
Allergic rhinitis	2.41	0.80-7.13	0.12	Ischemic heart disease	5.12	1.61-15.0	0.0070

Definition of abbreviations: OR = odds ratio; CI = confidence interval

airflow limitation (OR 0.58, 95% CI 0.07-4.57, p=1.00), smoking history (OR 1.93, 95% CI 0.79-4.75, p=0.16), plasma IgE (OR 1.00, 95% CI 0.85-1.10, per 100 μ/mL increase, p=0.94), cedar-pollen RAST value (OR 0.46, 95% CI 0.15-1.43, p=0.23), or house-dust RAST value (OR 1.68, 95% CI 0.62-4.58, p=0.39) were not associated with wheezing. We could not calculate the odds ratio between a history of ischemic heart disease and wheezing because two participants with a history of ischemic heart disease did not report wheezing.

In the participants aged 65 to 88 years old, a history of bronchial asthma (OR 4.49, 95% CI 1.44-14.00, p=0.017) and ischemic heart disease (OR 4.72, 95% CI 1.64-13.58, p=0.0081) were identified as being significantly associated with wheezing in the univariate analysis. However, other factors such as sex (men, OR 0.90 95%CI 0.41-1.96, p= 0.85), allergic rhinitis (OR 1.36, 95%CI 0.52-3.54, p=0.60), airway reversibility (OR 0.89, 95% CI 0.28-2.78, p=1.00), pre-bronchodilator airflow limitation (OR 2.40, 95% CI 0.98-5.84, p=0.058), smoking history (OR 1.66, 95% CI 0.71-3.85, p=0.24), plasma IgE (OR 0.96, 95% CI 0.80-

1.05, per 100 μ/mL increase, p=0.58), cedar-pollen RAST value (OR 0.25, 95% CI 0.03-1.90, p=0.22), or house-dust RAST value (OR 1.64, 95% CI 0.52-5.15, p=0.33) was not associated with wheezing.

Table 4 shows the multivariate analyses to detect the factors which associate with wheezing in each group divided by age. In the participants aged 45 to 64 years, wheezing was associated with sex (men, OR 3.12, 95%CI 1.10-9.67, p=0.0033) and the history of bronchial asthma (OR 22.32, 95%CI 6.50-83.96, p<0.0001). In the participants aged 65 to 88, wheezing was associated with the history of bronchial asthma (OR 4.86, 95%CI 1.39-15.13, p=0.015) and the history of ischemic heart disease (OR 5.12, 95%CI 1.61-14.97, p=0.0070).

We measured the plasma NT-pro-BNP levels in twenty-one participants with a history of ischemic heart disease (aged 60 to 84 years) and in thirty-five age matched participants with no history of ischemic heart disease (aged 60 to 86 years) in order to evaluate the association between wheezing and heart disease. Participants with both a history of ischemic heart disease and wheezing showed significantly
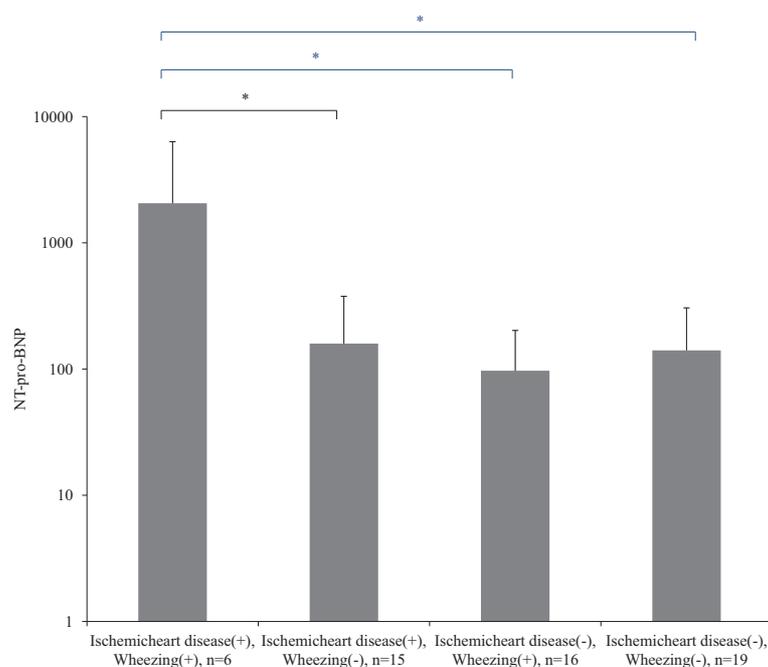
Figure 1. Plasma NT-pro-BNP levels in the twenty-one participants with a history of ischemic heart disease and the age-matched thirty-five participants without a history of ischemic heart disease. Those participants were classified into four categories based on the presence of ischemic heart disease and/or wheezing. p=0.0065, ANOVA. *p<0.05, Tukey's test.

Table 5. Multivariate Analyses to Assess the Relationship between Airway Reversibility and a History of Diseases

Variables	OR	95% CI	p
Age	1.00	0.97-1.02	0.91
Men	1.14	0.69-1.85	0.61
Pre-bronchodilator airflow limitation	4.58	2.50-8.39	<0.0001
Ischemic heart disease	4.65	1.26-17.6	0.022

Definition of abbreviations: OR = odds ratio; CI = confidence interval

higher plasma levels of NT-pro-BNP than the other three groups (Fig. 1).

In univariate analysis, we found no significant association between airway reversibility and wheezing (OR 0.71, 95%CI 0.29-1.75, p=0.54) or a history of asthma (OR 1.19, 95%CI 0.47-3.05, p=0.80). However, a history of ischemic heart disease (OR 5.25, 95%CI 1.56-17.61, p=0.0093), pre-bronchodilator airflow limitation (OR 4.65, 95%CI 2.58-8.39, p<0.0001) was associated with reversibility. In the multivariate analysis, pre-bronchodilator airflow limitation (OR 4.58, 95%CI 2.50-8.39, p<0.0001) and a history of ischemic heart disease (OR 4.65, 95% CI 1.26-17.62, p= 0.022) was found to be independently associated with airway reversibility (Table 5).

Discussion

The present study demonstrated that wheezing in the population aged 45 to 64 years was associated with bronchial asthma and gender, and wheezing in the population aged 65 to 88 years was associated with a history of bronchial asthma and ischemic heart disease in a Japanese local community. In addition, a history of ischemic heart disease was associated with airway reversibility. Although it is well known that wheezing in elderly people contributes not only to bronchial asthma but also to acute heart failure at the primary care setting (15), it has been confirmed that a history of ischemic heart disease is an important cause of wheezing at the population-based setting.

Wheezing is often observed in patients with dyspnea due to heart failure (16). The mechanism of wheezing in heart failure is considered to be due to congestion of bronchial vessels, which leads to edema and thickening of bronchial wall (12). Furthermore, it has been reported that impaired left ventricular function can cause an abnormality of pulmonary function, such as airway hyper-responsiveness or restrictive and obstructive dysfunction (17). Hyper-responsiveness in patients with heart failure is considered to

be mediated by distention of bronchial vessels with bronchial submucosal edema which is accentuated by methacholine, and the obstruction is partially corrected by the administration of bronchodilator (17).

In the present study, it was shown that a history of ischemic heart disease but not asthma was associated with airway reversibility. Witte et al reported that bronchodilators reverse the increased airway resistance in chronic heart failure (18). Thus it is possible that airway reversibility is correlated with heart function in participants with a history of ischemic heart disease. That is very important in the clinical setting. If a patient complains of wheezing and the pulmonary function test reveals airway reversibility, his or her diagnosis would be not only asthma but also cardiac disease, especially in the elderly. The rapid check of serum NT-proBNP would be beneficial for the differential diagnosis between asthma and heart disease (19). On the other hand, we could not find a relationship between a history of asthma and airway reversibility. Among the 31 participants who had a history of asthma, 8 of them (27.6%) had been taking asthma medication and 21 of them (72.4%) had not been taking asthma medication at the survey time point. We consider that asthma medication may affect the relationship between a history of asthma and airway reversibility.

It has been reported that subjective symptoms, including wheezing, are related to QOL more closely than objective parameters, such as FEV_1, in a population aged between 20 and 44 years (20). The authors of that study speculated that the underlying problem in the population was bronchial asthma. More recently, Voll-Aanerud et al reported that respiratory symptoms in adults were related to impaired QOL, regardless of diagnosis of asthma or COPD (21). Consistent with these studies, our results revealed that a lower QOL was not associated with impaired lung function but it was associated with wheezing in the study population.

In the present study, a history of allergic rhinitis was associated with wheezing in the univariate analysis. The frequent coexistence of asthma and allergic rhinitis has been reported (22), and allergic rhinitis is a risk factor for developing bronchial asthma (23, 24). However, it was rarely reported that allergic rhinitis was related to wheezing. Lee et al investigated the risk factors of wheezing in Korean military personnel. They reported that current wheeze was strongly associated with current allergic rhinoconjunctivitis (25). The present results also suggest that there would be a relationship between wheezing and rhinitis.

Because wheezing is a common clinical finding in patients with COPD, we expected that a higher proportion of wheezing participants would have COPD (26). One of the major criteria of COPD is post-bronchodilator airflow limitation (27). However, we did not find an association between wheezing and post-bronchodilator airflow limitation. Among our participants who met the lung function criteria of COPD, the mean (SD) FEV_1%pred was 87.3% (18.8) (data not shown). That meant that most of them, even if they would have COPD, had relatively mild diseases, GOLD

stage I or II (28). That may be the reason why we could not find an association between wheezing and post-bronchodilator airflow limitation. On the other hand, the elder asthmatics might be complicated with COPD. As mentioned above, we did not differentiate the two diseases. However, we performed an airway reversibility test in 27 of 31 asthmatic participants. Only 3 of them showed postbronchodilator airway obstruction (COPD criteria). Those 3 participants showed mild postbronchodilator obstruction (FEV_1%pred>75%). Therefore, the effect of COPD on asthmatics in this study seemed to be minimal.

This study has some limitations. First, the survey was not distributed randomly but rather was given to individuals volunteering to participate. This may have introduced a bias into the study. However, the prevalence of wheezing and asthma in this study is not far from the results of our previous study in which the response rate was 78.9% (8). And the proportion of subjects aged 60 or over in this study was similar with that in the local population. Thus we believe that our findings can be generalized to the elderly in the community. Second, the diagnosis of asthma or ischemic heart disease was based on participants recall. That was not a complete diagnosis and there might be errors in some cases. To compensate for this possibility, we measured serum NT-proBNP levels. We detected the association between a history of ischemic heart disease and a high level of serum NT-proBNP. These findings might imply impaired heart function in participants with a history of ischemic heart disease. Third, most of the participants with suspected COPD from airflow limitation revealed relatively mild dysfunction as mentioned above. And the prevalence of participants who met COPD criteria of airflow limitation was lower than that of a previous Japanese survey (29). We must bear in mind the possibility that individuals with more severe COPD did not participate in this study.

Conclusion

Wheezing in the population aged 45 to 64 years was associated with bronchial asthma, and in the population aged 65 years and over, it was equally associated with both bronchial asthma and ischemic heart disease. Airway reversibility, which was present in 19.5% of our population, was associated with a history of ischemic heart disease. It is suggested that bronchial asthma and heart disease are both significant causes of wheezing and affect the QOL in the elderly of Japanese local community.

The authors state that they have no Conflict of Interest (COI).

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