



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Original Article

Allergic bronchopulmonary aspergillosis in Japan: A nationwide survey

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ARTICLE INFO

Article history:

Received 26 December 2016

Received in revised form

2 April 2017

Accepted 13 April 2017

Available online xxx

Keywords:

Allergic bronchopulmonary aspergillosis

Aspergillus

Bronchiectasis

Immunoglobulin E

Schizophyllum commune

Abbreviation:

ABPA, allergic bronchopulmonary

aspergillosis; ABPM, allergic

bronchopulmonary mycosis; CB, central

bronchiectasis; CT, computed tomography;

GINA, Global Initiative for Asthma;

HAM, high attenuation mucus;

IgE, immunoglobulin E; IQR, interquartile

range

ABSTRACT

Background: Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease characterized by a hypersensitivity reaction to *Aspergillus* species colonizing the airways. The clinical characteristics of ABPA may differ depending on genetic and environmental background. We performed a nationwide survey to determine the clinical characteristics of ABPA in Japan.

Methods: In 2013, a questionnaire on physician-diagnosed ABPA/allergic bronchopulmonary mycosis was sent to 903 medical centers specializing in respiratory or allergic diseases. Cases fulfilling the following criteria were categorized as possible ABPA-central bronchiectasis (ABPA-CB): 1) presence of specific serum immunoglobulin E (IgE) antibodies or a positive skin reaction to *Aspergillus*, and 2) bronchiectasis or mucoid impaction in the central bronchi.

Results: Of 499 physician-diagnosed cases reported by 132 clinical centers, 358 cases met the criteria for possible ABPA-CB. Median age of ABPA-CB onset was 57 (interquartile range, 44–68) years; later-onset disease, developing ≥ 50 years of age, accounted for 66% of the cases and was associated with female sex, delayed onset of asthma, and lower levels of serum IgE. A third of the patients (120 patients, 34%) exhibited low levels of serum total IgE (<1000 IU/mL). *Aspergillus* species were isolated from sputum in 126/213 cases (59%), and *Schizophyllum commune* was identified in 12 (6%) patients. During the course of the treatment, ABPA recurred in 169 (48%) cases.

Conclusions: This nationwide survey identified several unique clinical characteristics of ABPA in Japan, such as late-onset, relatively lower serum IgE levels, and frequent recurrences/flare-ups.

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Introduction

Aspergillus species (spp.) colonizing the airways can induce type I and III hypersensitivity reactions and eventually cause allergic bronchopulmonary aspergillosis (ABPA) in patients with asthma or

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Peer review under responsibility of Japanese Society of Allergology.

<http://dx.doi.org/10.1016/j.alit.2017.04.011>

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cystic fibrosis. Clinical characteristics of the disease include peripheral and systemic eosinophilia, increased levels of serum immunoglobulin E (IgE), pulmonary infiltrates, and bronchiectasis/mucoid impaction in the central bronchi.

It is estimated that the global burden of ABPA is 1.4–6.8 million patients.¹ However, the prevalence of ABPA among the asthmatic population varies significantly according to the area studied; the following prevalence rates have been reported: 2.5% in China, 2.7% in Saudi Arabia, 4.9% in New Zealand, and 7–22% in India.² Reported total serum IgE levels, an essential biomarker for the diagnosis and evaluation of disease activity, also vary considerably, and studies have found median IgE levels of 676 IU/mL (UK), 2760 IU/mL (Australia), and 6434 IU/mL (India).^{3–5} These variations may be due to differences in genetic background among the populations or differences in environmental and social factors such as temperature, humidity, sanitary conditions within the home setting. Recently, several epidemiological studies published in Korea and Japan have highlighted several unique clinical characteristics of ABPA in this region, such as older age of ABPA onset.^{6–10} However, these are relatively small, single-center studies, and a large-scale, multi-center study is required to characterize the clinical presentation of ABPA in East Asia. We performed a nationwide survey in Japan to identify the unique clinical features of ABPA in East Asia.

Methods

Subjects

This study is based on a retrospective, cross-sectional survey of ABPA and allergic bronchopulmonary mycosis (ABPM) caused by non-*Aspergillus* fungi in Japan, conducted between September and

November 2013. A questionnaire was sent to 903 departments or centers certificated by the Japanese Respiratory Society or the Japanese Society of Allergology in order to collect data on the clinical characteristics of physician-diagnosed ABPA/ABPM in Japan. The parameters at the diagnosis of ABPA/ABPM evaluated in the questionnaire were as follows: age; sex; age at ABPA/ABPM onset; comorbidities such as physician-diagnosed asthma and its age at onset and severity; laboratory data including total and *Aspergillus*-specific IgE levels, *Aspergillus* antigen skin test, precipitating and IgG antibodies to *Aspergillus* spp., fungal sputum cultures; thoracic computed tomography (CT) findings including central bronchiectasis (CB), mucoid impaction, high attenuation mucus (HAM) in the central airways, infiltrates, ground glass opacity, and cystic/fibrotic changes in the lungs. Information about treatment and prognosis was also collected including the drugs used for treatment and the duration of treatment with corticosteroids, anti-fungal agents, anti-IgE antibodies, and the recurrence/flare of the disease. Asthma severity was defined by the treatment step required to control asthma, according to the updated version of the 2016 statement by the Global Initiative for Asthma (GINA).¹¹ The recurrences/flare of ABPA were judged by each physician, based on worsening of symptoms, radiographic findings, and/or laboratory data such as an increase in total IgE levels in serum.

This study was approved by the Institutional Review Board of Tokai University School of Medicine (#13R-105), and implemented in compliance with the Declaration of Helsinki.

Definition of possible ABPA-CB

The study design reflected real-world management of ABPA/ABPM and, in a substantial number of cases, data were incomplete

Table 1
Demographic and laboratory data of the patients with possible ABPA-central bronchiectasis.

	ABPA-central bronchiectasis		p*
	All cases	HAM (+) (-)	
n (%)	358	148 (41)	210 (59)
Age, y	64 (51–72)	62 (51–71)	65 (51–73)
Women	57%	67%	50%
Asthma	81%	78%	83%
Age at onset ^a , y	37 (10–55)	38 (11–58)	37 (10–54)
Early-onset asthma (<16 y)	28%	27%	29%
Late-onset asthma (≥50 y)	33%	40%	29%
Treatment step at diagnosis ^b 1–2/3/4/5, %	24/30/28/17	28/33/26/14	22/29/30/19
ABPA			
Age at onset, y	57 (44–68)	59 (43–68)	56 (44–68)
Duration between onset of asthma and ABPA ^c , y	14 (2–31)	9 (1–27)	16 (2–34)
Laboratory data at diagnosis			
Peripheral blood eosinophil counts ^d (/μL)	1075 (640–1797)	1166 (661–1810)	990 (544–1793)
Serum IgE levels (IU/mL)	1913 (758–5555)	1780 (692–4963)	2105 (773–6052)
Sputum culture ^e			
<i>Aspergillus</i> spp.	59%	63%	57%
<i>Shizophyllum commune</i>	6%	11%	2%
Thoracic CT findings			
Infiltration/GGO	88%	89%	88%
Cystic/fibrotic change	13%	18%	9%
Therapy			
Oral corticosteroids	75%	84%	69%
Anti-fungal drugs	56%	62%	53%
Anti-IgE antibody	6%	6%	6%
Recurrence/flare	48%	45%	49%

Values are medians (interquartile range) or proportion of patients in each study groups if not otherwise specified. n = 349–358, except for ^a n = 271, ^b n = 240, ^c n = 263, ^d n = 194, ^e n = 213.

*HAM (+) vs. HAM (-). ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; GGO, ground glass opacity; HAM, high attenuation mucus; IgE, immunoglobulin E.

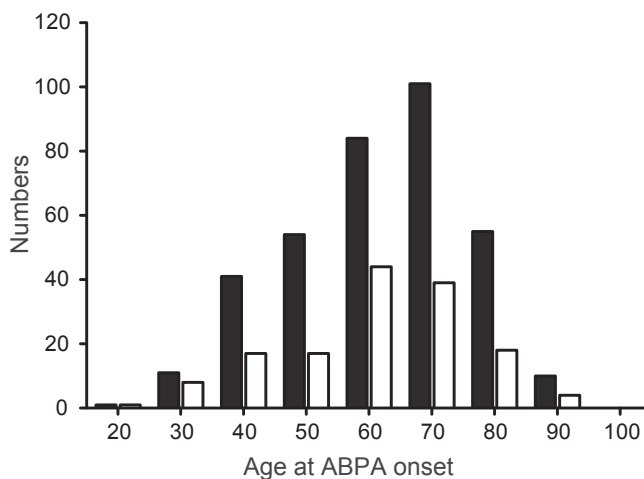


Fig. 1. Age at onset of ABPA in Japan. The distribution of age of onset was demonstrated for the cases with ABPA-central bronchiectasis (closed bars) and ABPA with high attenuation mucus (open bars).

lacking the parameters required for diagnosis based on the established criteria,^{2,12,13} such as the skin test, precipitating antibody levels or levels of IgG to *Aspergillus*. We, therefore, applied two minimal criteria to define possible ABPA-CB: 1) a positive type I hypersensitivity reaction to *Aspergillus fumigatus*, confirmed by *A. fumigatus*-specific IgE antibody in the serum or an immediate skin reaction to *A. fumigatus* antigen; and 2) presence of bronchiectasis or mucoid impaction in the central bronchi on the thoracic CT scan.

In order to validate the rationale for this definition, we also analyzed the cases diagnosed using more specific criteria for ABPA-CB: positive type I sensitivity to *A. fumigatus* in combination with confirmation of HAM, a highly specific sign of ABPA,^{5,14} in the central bronchi (ABPA-HAM).

Statistical analysis

Numerical data are presented as median and interquartile range (IQR), and categorical data are presented as numbers/percentages. Categorical variables were compared using Fisher's exact test, while continuous variables were compared using the Mann–Whitney *U* test. Statistical analysis was performed using the IBM SPSS statistics ver. 21 (IBM, Chicago, IL, USA). The results were two-sided, and a *p* value <0.05 was considered statistically significant.

Results

A total of 499 cases of physician-diagnosed ABPA/ABPM were reported from 132 clinical centers. Of these, 12 cases were omitted from the analysis because the thoracic CT scan had not been performed. Serum *A. fumigatus*-specific IgE antibody was positive in 346 cases, and skin test for *Aspergillus* antigen confirmed type I hypersensitivity in further 14 cases. Central bronchiectasis and mucoid impaction were identified in 318 and 288 cases, respectively. A total of 358 cases met the criteria of possible ABPA-CB and HAM was identified in 148 cases (41%) among the ABPA-CB cases.

Demographic data and clinical characteristics of these patients are shown in Table 1. Eighty-one percent of the cases had presented with asthma as a predisposing condition, and approximately a half of them required step 4 or 5 treatment to control their asthma prior to the development of ABPA. Compared to ABPA-CB without HAM, ABPA-HAM was associated with the following: female predominance (67% vs. 50%, *p* = 0.002), more frequent identification of *Schizophyllum commune* in sputum cultures (11% vs. 2%, *p* = 0.02), presentation of cystic/fibrotic changes on thoracic CT (18% vs. 9%, *p* = 0.009), and increased requirement for corticosteroid treatment (84% vs. 69%, *p* = 0.001) (Table 1).

Median age of possible ABPA-CB onset was 57 (IQR, 44–68) years and 66% of the patients developed ABPA-CB at ≥50 years of age (Table 1; Fig. 1). Sixty-nine percent of the patients with ABPA-

Table 2

Differences in clinical characteristics according to age and serum IgE levels at the onset of possible ABPA-central bronchiectasis.

	Age at onset of ABPA(y)		Serum IgE (IU/mL)	
	<50	≥50	<1000	≥1000
n (%)	120 (34)	229 (66)	113 (32)	241 (68)
Age, y	45 (40–52)	69 (62–75)	63 (53–71)	64 (49–73)
Women	43%	66%*	70%	52%*
Asthma	88%	77%*	84%	80%
Age ^a at onset, y	16 (5–32)	52* (32–63)	47 (31–61)	30*(8–50)
Early-onset asthma (<16 y)	50%	13%*	16%	34%*
Late-onset asthma (≥50 y)	0%	55%*	46%	27%*
ABPA				
Age at onset, y	39 (32–44)	65* (57–65)	57 (46–67)	56 (41–68)
Duration between on-set of asthma and ABPA ^b , y	16 (5–29)	11 (1–34)	8 (0–17)	18* (4–35)
Laboratory data at diagnosis				
Peripheral blood eosinophil counts ^c (/μL)	1153 (666–2121)	1021 (634–1752)	1071 (638–1496)	1065 (626–1849)
Serum IgE levels (IU/mL)	2897 (816–7051)	1660* (681–4665)	488 (265–698)	3590* (1857–7760)
Sputum culture ^d				
<i>Aspergillus</i> spp.	56%	62%	54%	62%
<i>Schizophyllum commune</i>	4%	7%	5%	6%
Thoracic CT findings				
Infiltration/GGO	90%	87%	85%	89%
Cystic/fibrotic change	12%	13%	13%	12%
Therapy				
Oral corticosteroids	80%	73%	79%	74%
Anti-fungal drugs	56%	57%	57%	58%
Recurrence/flare	51%	47%	42%	51%

Values are medians (interquartile range) or proportion of patients in each study groups if not otherwise specified. n = 342–354, except for ^a n = 264–268, ^b n = 260–263, ^c n = 191–192, ^d n = 210.

**p* < 0.05; age at onset of ABPA <50 vs. ≥ 50, or serum IgE <1000 vs. ≥ 1000 IU/mL.

ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; GGO, ground glass opacity; IgE, immunoglobulin E.

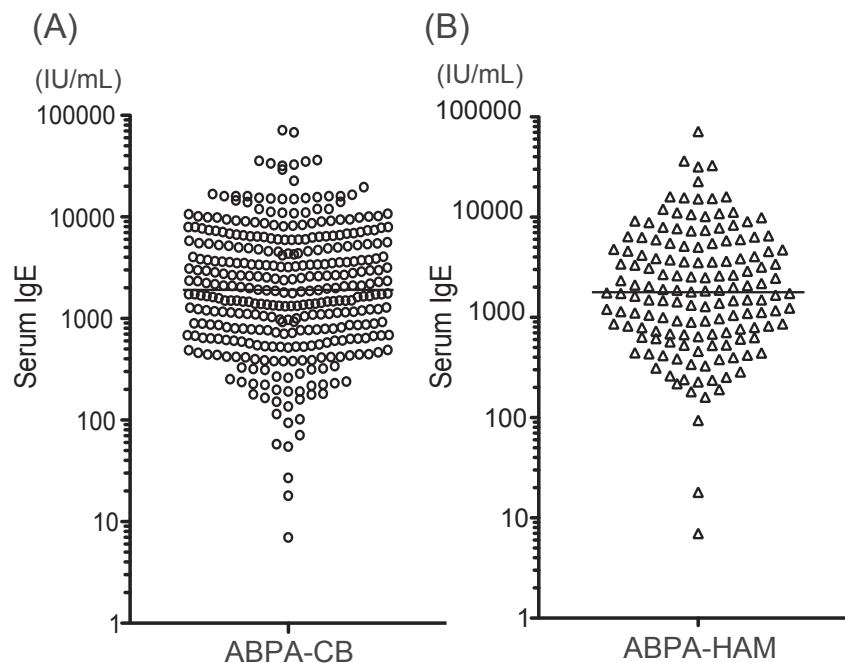


Fig. 2. Total IgE levels in serum from Japanese patients with ABPA. Serum IgE levels in patients with ABPA-central bronchiectasis (ABPA-CB, **A**) and ABPA-CB with high attenuation mucus (ABPA-HAM, **B**). The bars indicate median values.

Table 3
Differences of characteristics and laboratory data by recurrence/flare in the patients with possible ABPA-central bronchiectasis.

	Recurrence/flare		<i>p</i> [*]
	(–)	(+)	
n (%)	185 (52)	169 (48)	
Age, y	64 (50–72)	63 (52–72)	0.85
Women	57%	58%	0.83
Asthma	77%	85%	0.08
Age at onset ^a , y	41 (15–59)	32 (10–54)	0.05
Early-onset asthma (<16 y)	25%	30%	0.42
Late-onset asthma (≥50 y)	37%	30%	0.24
ABPA			
Age at onset, y	59 (44–69)	55 (42–65)	0.03
Duration between on-set of asthma and ABPA ^b , y	13 (1–31)	15 (2–34)	0.33
Laboratory data at diagnosis			
Peripheral blood eosinophil counts ^c (/μL)	1134 (642–2136)	1029 (631–1653)	0.33
Serum IgE levels (IU/mL)	1728 (686–4561)	2339 (820–6853)	0.05
Sputum culture ^d			
<i>Aspergillus</i> spp.	69%	51%	0.02
<i>Shizophyllum commune</i>	2%	10%	0.03
Thoracic CT findings			
Infiltration/GGO	86%	91	0.14
Cystic/fibrotic change	12%	13	0.88
Therapy			
Oral corticosteroids	71%	82%	0.01
Anti-fungal drugs	60%	55%	0.39
Anti-IgE antibody	4%	8%	0.13

Values are medians (interquartile range) or proportion of patients in each study groups if not otherwise specified. n = 345–354, except for ^a n = 269, ^b n = 261, ^c n = 193, ^d n = 210.

ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; GGO, ground glass opacity; IgE, immunoglobulin E.

* Recurrence/flare (+) vs. (–).

HAM also developed the disease at ≥ 50 years (Fig. 1). There was no case of patients <15 years at onset of ABPA. Later-onset disease, developing ≥50 years, was more common in women, was less frequently associated with asthma, particularly childhood-onset

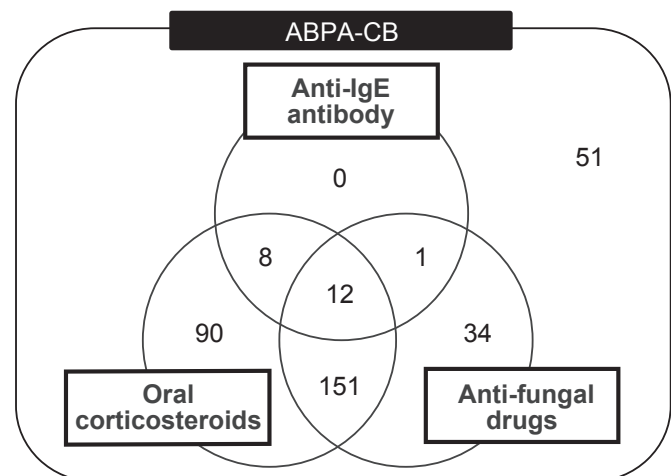


Fig. 3. Treatment of ABPA in Japan. The Venn diagram shows the numbers of patients with possible ABPA-central bronchiectasis, who were untreated or treated with oral corticosteroids, anti-fungal agents, and/or anti-IgE antibody.

asthma, and exhibited lower levels of serum IgE (Table 2). Among patients with ABPA-HAM, there still was a significant association between later-onset ABPA and sex or the age of asthma onset (Supplementary Table 1).

Median total serum IgE levels were 1913 IU/mL in patients with ABPA-CB and 1780 IU/mL in patients with ABPA-HAM (Table 2; Fig. 2). In approximately a third of cases with ABPA-CB or ABPA-HAM, IgE levels were <1000 IU/mL (Table 2, Supplementary Table 1). Low IgE levels (<1000 IU/mL) associated with female sex and later-onset asthma in patients with ABPA-CB, but not in patients with ABPA-HAM. Precipitating antibodies against *A. fumigatus* were examined in 240 cases (66%), and 73% of cases showed positive results. No differences were found in sex, age at onset of asthma or ABPA, total IgE levels, thoracic CT findings,

treatment, or rate of recurrences/flare, between the patients with positive and those with negative to precipitating antibodies. However, sputum cultures from patients with precipitating antibodies were more likely to be positive for *Aspergillus* spp. (Supplementary Table 2).

Sputum cultures were obtained in 213 cases and *Aspergillus* spp. were identified in 126 cases (59%), including *A. fumigatus* (33%), *A. niger* (6%), *A. terreus* (4%), and unspecified *Aspergillus* spp. (16%). *S. commune*, a Homobasidiomycete known to cause ABPM, was identified in 12 cases, who were more likely to demonstrate HAM on thoracic CT (Table 1) and recurrences/flare of ABPA (Table 3).

Oral corticosteroids, anti-fungal agents, and anti-IgE antibodies (omalizumab) were added in 75%, 56%, and 6% of patients, respectively, following the diagnosis of ABPA-CB, whereas no additional treatment was administered in 14% of patients (Fig. 3). Combined treatment with oral corticosteroids and anti-fungal agents was administered in 46% of patients. During the course of treatment, recurrences/flare occurred in 48% of ABPA-CB cases and 46% of ABPA-HAM cases (Table 3, Supplementary Table 3). Recurrence/flare in ABPA-CB cases was associated with younger age of ABPA onset, higher serum IgE levels at primary diagnosis, positive cultures for *S. commune*, and treatment with systemic corticosteroids (Table 3). However, among the ABPA-HAM patients, the only association demonstrated in this study was between recurrence/flare and treatment with systemic corticosteroids (Supplementary Table 3).

Discussion

This is the first nationwide survey of ABPA in Japan and one of the largest studies examining the clinical characteristics of this disease worldwide.^{5,8,13,15–19} This study has demonstrated several unique clinical characteristics of ABPA-CB in Japan: older age at onset, a subpopulation with lower serum IgE levels, and frequent recurrence.

Our study showed that the median patient age at ABPA-CB onset was 57 years; this is older than the data reported previously from other countries. The median age of ABPA-CB onset were 34 and 36 years in two Indian studies, 41 years in a Chinese study and 47 years in a UK study.^{15,16,20,21} In contrast, a Korean study and two single center Japanese studies demonstrated a relatively older age at ABPA onset, 63, 57, and 57 years, respectively.^{8–10} These findings, coupled with our observations, suggest that the elderly population with asthma is vulnerable to ABPA in Japan and Korea. There are two possible reasons for the high rate of late-onset ABPA in these countries, which may associate with 1) the higher prevalence of later-onset asthma in these countries,^{22–25} or 2) the increased number of patients undergoing long-term inhaled corticosteroid therapy. Our data demonstrated that later-onset ABPA was associated with delayed-onset asthma; median age of asthma onset was 52 years compared to 16 years in later- and early-onset ABPA, respectively, suggesting that high prevalence of later-onset asthma is associated with the higher rate of later-onset ABPA in Japan. On the other hand, the duration between the onset of asthma and ABPA was not significantly different between later- and early-onset ABPM (11 years vs. 16 years, respectively). Although the duration of asthma is not necessarily equal to the duration exposed to inhaled corticosteroids, it seems unlikely that long-term exposure to inhaled corticosteroids is the major reason of higher incidence of ABPA at later stage of life.

Our study found relatively lower levels of total IgE in the serum, particularly in patients with later-age onset disease.⁵ Total serum IgE levels of 417 IU/mL have been used as the cutoff level for ABPA in a classic criteria,¹² although recent studies suggest that a

higher cut-off value may be more appropriate. Agarwal *et al.* recommended a cut-off value of 2347 IU/mL and the International Society for Human and Animal Mycology recommended a cut-off value of 1000 IU/mL.^{2,26} In contrast, several reports from East Asian countries demonstrate relatively lower serum total IgE levels in patients with ABPA.^{8–10} Tanimoto reported median IgE level of 1170 IU/mL in Japanese patients with ABPA and Kim reported level of 927 IU/mL in Korean patients.^{8–10} In our study, later-onset disease was associated with lower levels of total serum IgE, suggesting that the higher prevalence of later-onset disease may be one of the reasons for the lower IgE levels in ABPA in East Asian countries, such as Korea and Japan.

Profiles of fungi isolated from sputum were another unique finding in the current survey of Japanese ABPA. *S. commune* was identified in sputum cultures from 12 cases, even in the presence of hypersensitivity to *Aspergillus*. In a recent review of non-*Aspergillus* ABPM, *S. commune* was the third most common fungus causing ABPM, followed by *Candida* spp. and *Bipolaris* spp.²⁷ Although *S. commune* is found worldwide, all cases of *S. commune*-associated ABPM were reported in Japan, with the exception of an Indian case. There may be specific genetic or environmental backgrounds that favor the development of this condition in Japan. Our data showing the discrepancy between fungus-specific IgE and microbial examination also raised the issue of the difficulty to identify the fungus causing ABPA/ABPM and the possibility of microbial substitution, as we have previously reported.²⁸

In this study, recurrence/flare of ABPA-CB was observed in 169 cases (48%), a higher rate than that reported in previous studies,^{5,29} possibly due to the inclusion of flare episodes in corticosteroid-naïve patients in addition to recurrences in the present study. Patients who experienced recurrence/flare of the disease had increased total IgE levels. In addition to its usefulness as a biomarker to monitor disease activity,²⁹ total IgE levels at diagnosis may be a useful biomarker to predict prognosis of ABPA. However, prospective studies will be required, as this study did not reproduce the positive correlation between the recurrence/flare rates and total serum IgE levels in ABPA-HAM patients. Agarwal *et al.* demonstrated that relapse frequency of ABPA is associated with HAM and aspergilloma,⁵ although there was no difference in the frequency of recurrence/flare between ABPA patients with and without HAM in the present study.

There are a number of limitations of this study. This is a retrospective study of real-world practice, and there may have been some selection bias; uncertainty in the diagnosis of ABPA and comorbid diseases such as asthma; incomplete data collection due to limited availability and quality of some laboratory tests such as the precipitating antibody/IgG to *Aspergillus* and sputum culture. Therefore, in the present study, we used two minimal criteria to diagnose possible ABPA-CB. There may have been some cases with severe asthma with fungal sensitization accompanied by bronchiectasis included in the analysis, however, we believe that our conclusion, derived from our definition of possible ABPA-CB, is valid. Firstly, because ABPA-CB with and without precipitating antibodies showed equivalent clinical phenotypes, except for the results of sputum cultures. Secondly, because ABPA with HAM, which is a more specific characteristics of ABPA, yielded comparable results, particularly age of ABPA onset, total serum IgE levels, and recurrence/flare rates.

In conclusion, our nationwide survey has demonstrated several unique characteristics of ABPA in Japan, especially the presence of later-onset disease with lower levels of serum IgE. These patients are excluded from the diagnosis under the current criteria, and therefore, some modification of diagnostic criteria may be needed for this phenotype of ABPA.

Acknowledgments

We thank Ms. Naoko Yatabe and Mafumi Kawarabata for their excellent technical contributions to this study. We also thank all the physicians who cooperated in our nationwide survey of ABPA (See [Supplementary file: List of Collaborators](#)). This work was supported by Research Grant on Allergic Disease and Immunology from the Japan Agency for Medical Research and Development.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.04.011>.

Authors' contributions

TO had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting the manuscript. MT, TS, KK, HM, AH, NT, SK, KF, KH, JT, and KT contributed to the data entry, data interpretation, refining the study methodology, and manuscript review. KA contributed to the conception and design of the study, the supervision of all activities related to the conduct of the study, study idea, statistical analysis, discussion, writing, and final approval of the manuscript, and serve as the guarantor of the paper.

Conflict of interest

KA has received lecture fees from Astellas Pharma, Boehringer Ingelheim, Kyorin Pharmaceutical, MSD, Novartis Pharma, and research grant from Ono Pharmaceutical. MT has received lecture fees from AstraZeneca, Kyorin Pharmaceutical. HM has received lecture fees from AstraZeneca, Astellas Pharma, Kyorin Pharmaceutical, Boehringer Ingelheim, and MSD. The rest of the authors have no conflict of interest.

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Supplementary Table 1. Differences in clinical characteristics according to age and serum IgE levels at the onset of ABPA with high attenuation mucus.

	Age at onset of ABPA (y)		Serum IgE (IU/mL)	
	< 50	≥ 50	< 1,000	≥ 1,000
n (%)	45 (31)	101 (69)	50 (34)	98 (66)
Age, years	44 (38-49)	66* (61-73)	63 (54-71)	62 (49-72)
Women	53%	75%*	76%	63%
Asthma	84%	75%	84%	76%
Age at onset ^a , y	15 (14-30)	54* (33-63)	42 (18-62)	32 (10-55)
Early-onset asthma (< 16 years)	51%	12%*	22%	30%
Late-onset asthma (≥ 50 years)	0%	64%*	46%	37%
ABPA				
Age at onset, years	37 (28-41)	64* (58-70)	58 (44-68)	59 (42-68)
Duration between on-set of asthma and ABPA ^b , years	16 (4-27)	8 (0-30)	8 (0-22)	14 (1-31)
Laboratory data at diagnosis				
Peripheral blood eosinophil counts ^c (/μL)	1,134 (666-2,097)	1,181 (653-1,784)	787 (545-1,302)	1,181* (780-2,137)
Serum IgE levels (IU/mL)	1,872 (622-6,370)	1,737 (738-4,639)	494 (280-713)	3,546* (1,790-7,468)
Sputum culture ^d				
<i>Aspergillus</i> spp.	66%	63%	52%	67%
<i>Shizophyllum commune</i>	4%	14%	13%	10%
Thoracic CT findings				
Infiltration/GGO	91%	88%	86%	90%
Cystic/fibrotic change	22%	15%	18%	18%
Therapy				
Corticosteroids	91%	82%	84%	85%
Anti-fungal drugs	56%	65%	57%	64%
Recurrence/flare	47%	46%	44%	46%

Values are medians (interquartile range) or proportion of patients in each study groups if not otherwise specified. n = 142-148, except for ^a n = 103-104, ^b n = 103, ^c n = 82-83, ^d n = 85-86.

**p* < 0.05; age at onset of ABPA < 50 vs. ≥ 50, or serum IgE < 1,000 vs. ≥ 1,000 IU/mL.

ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; GGO, ground glass opacity; IgE, immunoglobulin E.

Supplementary Table 2. Differences of characteristics and laboratory data by the result of precipitating antibodies against *Aspergillus* in the patients with ABPA.

	ABPA-CB		ABPA-HAM	
	precipitating antibodies against <i>Aspergillus</i>		precipitating antibodies against <i>Aspergillus</i>	
	(-)	(+)	(-)	(+)
n (%)	65 (27)	175 (73)	23 (26)	65 (74)
Age, y	61(53-72)	64 (50-73)	62 (56-70)	62 (50-73)
Women	45%	57%	61%	66%
Asthma	83%	85%	74%	85%
Age at onset ^a , y	40 (20-56)	34 (10-56)	53 (25-68)	35 (10-58)
Early-onset asthma (< 16y)	23%	32%	19%	29%
Late-onset asthma (≥ 50 y)	31%	34%	56%	41%
ABPA				
Age at onset of ABPM, y	55 (46-67)	58 (41-68)	61 (55-68)	59 (41-69)
Duration between on-set of asthma and ABPA ^b , y	12 (2-30)	16 (4-34)	2 (0-24)	13 (1-26)
Laboratory data at diagnosis				
Peripheral eosinophil counts ^c (/μl)	910 (558-1,618)	1,028 (496-1,811)	758 (541-1,295)	1,200 (699-2,162)
Total IgE (IU/ml)	1,770 (750-3,606)	2,365 (781-6,447)	2,547 (729-7,700)	1,843 (658-5,712)
Sputum culture ^d				
<i>Aspergillus</i> spp.	30%	76%*	19%	83%*
<i>Shizophyllum commune</i>	22%	0%*	31%	0%*
Thoracic CT findings				
Infiltration/GGO	91%	89%	91%	92%
Cystic/fibrotic change	8%	13%	9%	23%
Therapy				
Corticosteroids	77%	76%	83%	92%
Anti-fungal therapy	52%	57%	50%	59%
Anti-IgE antibody	3%	6%	4%	5%
Recurrence/flare	59%	54%	57%	48%

Values are medians (interquartile range) or proportion of patients in each study groups if not otherwise specified. n = 235-240/87-88 for ABPA-CB/ABPA-HAM, respectively, except for ^a n

= 189/65, ^b n = 185/64, ^c n = 129/50, ^d n = 141/52.

*precipitating antibodies against *Aspergillus* (+) vs. (-).

ABPA, allergic bronchopulmonary aspergillosis; CB, central bronchiectasis; CT, computed tomography; GGO, ground glass opacity; HAM, high attenuation mucus; IgE, immunoglobulin E.

Supplementary Table 3. Differences of characteristics and laboratory data by recurrence/flare in the patients with ABPA with HAM.

	ABPA-HAM		<i>p</i> [*]
	Recurrence/flare		
	(-)	(+)	
n (%)	80 (54)	67 (46)	
Age, y	64 (51-71)	62 (49-72)	0.69
Women	61%	75%	0.08
Asthma	75%	84%	0.23
Age at onset ^a , y	36 (11-61)	40 (11-56)	0.76
Early-onset asthma (< 16 y)	27%	27%	1.00
Late-onset asthma (≥ 50 y)	40%	40%	1.00
ABPA			
Age at onset, y	60 (43-68)	56 (41-65)	0.19
Duration between on-set of asthma and ABPA ^b , y	10 (1-31)	8 (1-27)	0.49
Laboratory data at diagnosis			
Peripheral blood eosinophil counts ^c (/μL)	1,211 (643-2,961)	1,015 (701-1,536)	0.34
Serum IgE levels (IU/mL)	1,681 (698-4,459)	1,905 (682-6,000)	0.60
Sputum culture ^d			
<i>Aspergillus</i> spp.	73%	54%	0.08
<i>Shizophyllum commune</i>	5%	17%	0.08
Thoracic CT findings			
Infiltration/ GGO	88%	91%	0.60
Cystic/fibrotic change	18%	19%	0.83
Therapy			
Corticosteroid steroid	79%	92%	0.02
Anti-fungal therapy	65%	59%	0.49
Anti-IgE antibody	3%	10%	0.08

Values are medians (interquartile range) or proportion of patients in each study groups if not otherwise specified. n = 143-147, except for ^a n = 104, ^b n = 103, ^c n = 83, ^d n = 85.

* Recurrence/flare (+) vs. (-)

ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; GGO, ground glass opacity; HAM, high attenuation mucus; IgE, immunoglobulin E.

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