Received: 31 October 2017 | Revised: 28 May 2018 | Accepted: 1 June 2018

DOI: 10.1111/pai.12953

ORIGINAL ARTICLE

WILEY

Risk factors and impact of allergic bronchopulmonary aspergillosis in *Pseudomonas aeruginosa*-negative CF patients

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Abstract

Background: Allergic bronchopulmonary aspergillosis (ABPA) is a major complication in cystic fibrosis (CF) patients. Risk factors for ABPA and clinical deterioration in CF patients, negative for *Pseudomonas aeruginosa (Pa)*, were explored.

Methods: We performed a retrospective case-control study in 73 *Pa*-negative patients. Each patient was matched with 2 controls for age, gender, pancreas sufficiency, DeltaF508 mutation (homozygous or heterozygous), and *Pa* colonization.

Results: Median FEV_1 at the year of diagnosis (index year) was significantly lower in patients with ABPA. The median of cumulative values of FEV_1 and FVC before the index year was not significantly different. After the index year, the median of cumulative data for FEV_1 and FVC was significantly lower; there were significantly more hospitalization days and more IV antibiotic days compared to controls. Comparing pre- and post-index year data in patients with ABPA, significantly more hospitalization days and more IV antibiotic days were observed after the index year. During the period preceding the index year, significantly more ABPA patients were treated with rhDNase and inhaled corticosteroids.

Conclusions: Bronchial damage cannot be considered as a facilitating factor for ABPA. ABPA causes a significant increase in bronchial damage. In patients with ABPA, further bronchial damage can be controlled by an increase in hospitalization days and use of IV antibiotics. rhDNase and inhaled corticosteroids were associated with the development of ABPA.

KEYWORDS

allergic bronchopulmonary aspergillosis, *Aspergillus* colonization, *Aspergillus fumigatus*, *Aspergillus* sensitization, cystic fibrosis

1 | INTRODUCTION

Colonization with *Aspergillus fumigatus* (*Af*) is common in children with cystic fibrosis (CF). Since 2010, the yearly prevalence (at least one positive sputum culture per year) in Belgian patients varied between 28.5% and 34.9%.[1] The effect of *Af* colonization is well studied, but the results are equivocal. de Vrankrijker et al[2] did not find an independent association with more severe lung function decline, whereas Fillaux et al[3] reported the opposite data. Amin et al[4] identified *Af* colonization as a risk factor for hospitalization, and Hector et al[5] reported an increased risk of *Pa* infection in *Af*-colonized patients. Kraemer et al[6] and Agarwal[7] reported a pronounced deterioration in lung function in patients with ABPA. Kaditis et al[8] concluded that ABPA did not influence lung function decline. Although

it is widely assumed that ABPA has a deleterious effect on CF lungs, few separate data on the clinical impact in *Pa*-negative patients have been reported.

Allergic bronchopulmonary aspergillosis is a Th2-cell–mediated inflammatory response against *Af* antigens resulting in the production of *Af* specific immunoglobulin E (IgE) and immunoglobulin G (IgG) causing type I and type II hypersensitivity reactions, respectively. This complication has been recognized in severe allergic asthma (1%-2%), but the prevalence is higher in CF patients.[6] Relying on the Belgian CF register, the yearly incidence of ABPA in CF patients varies between 3.9% and 6.7%(data from 2010 to 2015).[1]There is no specific laboratory test available to establish the diagnosis of ABPA, and therefore, the disease entity is suspected on clinical grounds (wheezing, unclarified decline in lung function, recurrent need for IV antibiotics, lack of treatment success), indirect laboratory tests (total immunoglobulin E (IgE), *Af* specific RAST, precipitins, blood eosinophilia), and skipping consolidations on chest X-rays.[9]

The aim of this study was to explore risk factors and clinical deterioration in this specific patient group.

2 | METHODS

A retrospective longitudinal case-control study was designed relying on the Belgian CF register to reveal associated factors and consequences of ABPA in *Pa*-negative patients. The study was approved by the Local Ethics Committee of Ghent University Hospital, Belgium.

Patients with at least one episode of ABPA were selected out of the Belgian CF register, and matched with two control CF patients for age (±1 year), gender, pancreas sufficiency, DeltaF508 mutation (homozygous or heterozygous) for CFTR, and *Pa* colonization, relying on the European consensus. ABPA was defined according to the Cystic Fibrosis Foundation Consensus Conference criteria: acute or subacute clinical deterioration, total immunoglobulin E (IgE) >500 IU/mL, positive skin prick test or precipitins for *Af* increased *Af* specific immunoglobulin E (IgE).[7]

The Belgian CF register is a disease-specific register collecting annual clinical and demographic data from about 95% of people with CF living in Belgium. There are seven reference centers at ten clinics or sites that are obliged, by a convention with the National Institute for Health and Disability Insurance (NIHDI), to send the data to the registry. The NIHDI is a public social security institution that manages and supervises the compulsory health care and benefits insurance in Belgium. Under the convention, patients must be seen at least quarterly and have at least four sputum cultures taken not less than 1 month apart from each other during the year. Each of these visits is a multidisciplinary consultation.

Data on the index year and cumulative data were gathered from 3 years before the index year and 5 years after the index year. The index year is the year of ABPA diagnosis mentioned in the patient register.

The main characteristics that were compared are the percentage of predicted FEV_1 and FVC, hospitalization days, IV antibiotic days, the use of inhaled corticosteroids, rhDNase, azithromycin, and inhaled antibiotics. The percentage of predicted FEV_1 and FVC was calculated using the Wang[10] (males aged 6-17 years and females aged 6-15 years) and Hankinson[11] (males aged 18 years and older and females aged 16 years and older) equations, respectively.

Statistical analysis was performed using SAS®, version 9.3 (SAS Institute Inc. Cary, North Carolina USA). Descriptive results of baseline and clinical characteristics were expressed as frequencies (%) for discrete variables and mean (standard deviation) or median (interquartile range) for the count and continuous data.

Tests of association between discrete data were conducted using the chi-square statistic with Fisher's exact test, which is used for small counts (≤5) as needed. The count and continuous data did not satisfy the normality assumption so the Mann-Whitney two-sample rank test was performed to investigate the statistical differences between the study groups and for comparing the pre- and post-diagnosis period data. All tests were two-sided and considered statistically significant at alpha level <0.05.

3 | RESULTS

Seventy-three *Pa*-negative patients with ABPA were matched to 146 controls. Baseline characteristics are shown in Table 1.

The baseline characteristics at the index year in the *Pseudomonas aeruginosa*-negative group (Table 1) were similar to those in the ABPA cases and controls. At the index year (Table 2), patients with ABPA had significantly lower median FEV_1 values. Before the index year, the median of cumulative data (Table 3) revealed no significant differences in FEV_1 and FVC, hospitalization days, and IV antibiotic days. A progressive decrease in FEV_1 was noticed 2 years before the index year (Figure 1). After the index year, the median of cumulative

TABLE 1 Baseline characteristics at index year for *Pa*-negative ABPA and control patients

	ABPA cases	Controls	*P*-value
N	73	146	
Male	38 (52.1%)	76 (52.1%)	1
Adults	23 (31.5%)	47 (32.2%)	0.9184
Age y (median-IQR)	12.4 (9.6-20.5)	15.8 (11.8-22.4)	0.2572
DeltaF508 homozygous mutation	46 (63.0%)	92 (63.0%)	
Pseudomonas aeruginosa colonization	0 (100.0%)	0 (100.0%)	
PS	1 (1.4%)	2 (1.4%)	

ABPA, allergic bronchopulmonary aspergillosis; PS, pancreatic sufficiency n (%).

TABLE 2 Data at the index year in allergic bronchopulmonary aspergillosis (ABPA) patients and controls

	ABPA cases	Controls	*P*-value
N	73	146	
Percentage of predicted FEV_1	73.7 (49.6-88.5)	86.5 (60.1-96.2)	0.0186
Percentage of predicted FVC	89.4 (65.2-101.2)	91.0 (79.0-103.3)	0.3412
BMI *Z*-score	−0.7 (−1.4-0.3)	−0.5 (−1.2-0.3)	0.6258
CFRD	14 (19.2)	28 (19.2)	1.0000

Median (IQR).

data revealed significantly lower values for FEV_1 and FVC, more hospitalization days, and more IV antibiotic days (Table 4) in the ABPA group. Comparing the periods before and after the index years, patients with ABPA had significantly more hospitalization days, and more IV antibiotic days but no significant differences in lung function parameters after the index year (Table 5). This was not observed in the control group (data not shown). Cumulative data over the pre-index period showed the significantly higher use of inhaled corticosteroids and rhDNase (Table 6) in the ABPA group. After the index year, cumulative data showed significantly more ABPA patients treated with inhaled and systemic corticosteroids. Compared to the pre-index years, significantly more ABPA patients were treated with inhaled antibiotics, inhaled corticosteroids, and systemic corticosteroids during the post-index year (Table 7). No difference in treatment with azithromycin was observed before and after the index years.

4 | DISCUSSION

Allergic bronchopulmonary aspergillosis is a frequent complication in CF patients. It is suspected to have a harmful effect on lung function and to provoke serious bronchial damage.

Data on the index year in *Pa*-negative patients with ABPA revealed a significantly lower FEV_1 value. Colonization and sensitization to *Af* can already compromise lung function. de Vranckrijker et al[2] reported a higher prevalence of *Af* colonization in patients with more severe lung disease. Amin et al[4] described a difference of 3.6% in FEV_1 in *Af*-colonized patients. In ABPA patients and patients colonized with or sensitized for *Af*, Fillaux et al[3] observed a steeper lung function decline. The study of Kraemer et al[6] and Kaditis et al[8] showed lower initial FEV1 values at the moment of ABPA diagnosis. These studies were carried out on *Pa*-negative and *Pa*-colonized patients. Our data support this finding in *Pa*-negative patients. Significantly lower values for FEV1 at the index year could rely on the onset of ABPA during the preceding and ongoing years. The decrease seems to start 2 years before the year of ABPA diagnosis. The cumulative data before the index year did not reveal a higher need for treatment, suggesting a rather similar clinical status in patients and controls. The pronounced bronchial damage does not seem to be associated with a higher susceptibility to ABPA.

In accordance with Noni et al,[12] who reported a possible link between inhaled corticosteroids and ABPA, we found significantly more patients on inhaled corticosteroids in the pre-index period for the ABPA group; therefore, immunomodulation favoring *Af* colonization could be involved. Although wheezing as an early sign of ABPA could have induced the use of inhaled corticosteroids, the higher use during the pre-index years favors a possible immunologic link. The higher use of systemic corticosteroids relies on the start of the first-line treatment in patients with ABPA during the year of diagnosis (index year). Cumulative data before the index year revealed more patients with ABPA on rhDNase. As lung function parameters were not significantly different at the year of diagnosis, there is no

TABLE 3 Median, minimum-maximum values, and IQR of cumulative data before the index year in allergic bronchopulmonary aspergillosis patients and controls

Variable	Group	n	Median	Min	Max	IQR	Two-sided Pr > |Z|
FEV_1	Controls	252	85.3	16.7	136.0	60.1-97.4	0.0836
	Cases	132	79.0	19.6	133.2	65.3-90.5	
FVC	Controls	252	94.9	23.8	136.0	78.0-105.3	0.3649
	Cases	132	91.2	33.4	140.3	81.3-102.8	
All Hospitalization days	Controls	328	0.0	0.0	130.0	0.0-9.0	0.9379
	Cases	168	0.0	0.0	213.0	0.0-10.0	
All IV antibiotic days (home and hospital)	Controls	328	0.0	0.0	105.0	0.0-14.0	0.5301
	Cases	168	0.0	0.0	76.0	0.0-12.0	

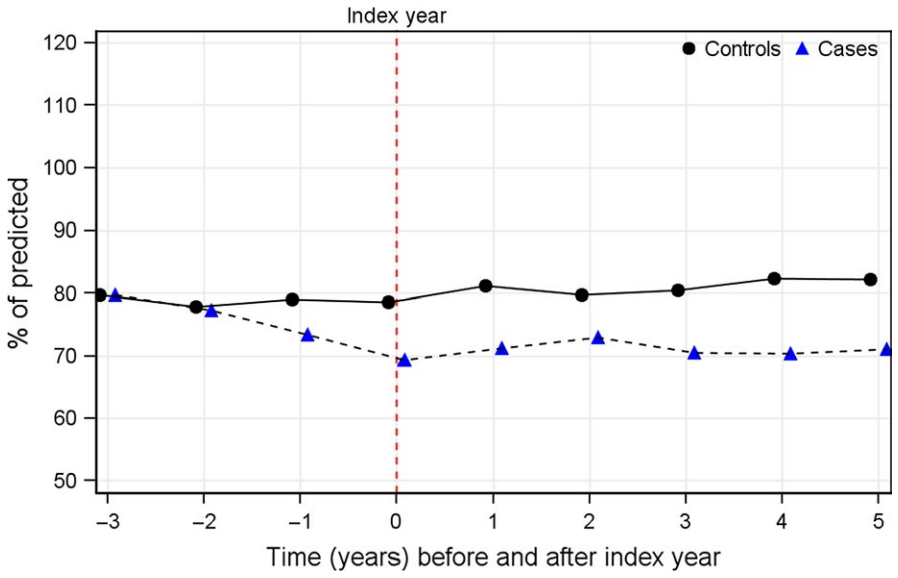

FIGURE 1 Mean FEV1 evolution over study time

TABLE 4 Median, minimum-maximum values, and IQR of cumulative values after the index year in ABPA cases and control

Variable	Period	Treat	Non-missing values	Median	Min value	Max value	IQR	Two-sided Pr > |Z|
FEV1	Post-index	Controls	72	86.1	12.4	123.2	71.4-105.9	<0.0001
	Post-index	Cases	304	69.0	16.9	137.4	49.3-84.6	
FVC	Post-index	Controls	72	101.0	23.0	125.1	91.5-107.6	<0.0001
	Post-index	Cases	305	87.6	26.7	138.1	71.2-100	
All Hospitalization days	Post-index	Controls	103	0.0	0.0	41.0	0-3	<0.0001
	Post-index	Cases	311	5.0	0.0	200.0	0-21	
All IV antibiotic days (home and hospital)	Post-index	Controls	82	0.0	0.0	70.0	0-0	<0.0001
	Post-index	Cases	268	14.0	0.0	138.0	0-33.5	

TABLE 5 Median, minimum-maximum values, and IQR of cumulative data in ABPA cases before and after the index years

Variable	Period	n	median	Min	Max	IQR	Two-sided Pr > |Z|
FEV1	Pre-index	132	79.0	19.6	133.2	65.3-90.5	0.0582
	Post-index	320	74.1	14.4	121.5	51.7-90.3	
FVC	Pre-index	132	91.2	33.4	140.3	81.3-102.8	0.4782
	Post-index	320	91.2	26.7	158.9	75.3-102.9	
All Hospitalization days	Pre-index	168	0.0	0.0	213.0	0.0-10.0	0.0295
	Post-index	361	0.0	0.0	256.0	0.0-14.0	
All IV antibiotic days (home and hospital)	Pre-index	168	0.0	0.0	76.0	0.0-12.0	0.0044
	Post-index	361	0.0	0.0	131.0	0.0-15.0	

obvious explanation for this result. The hypothesis of Jubin et al[13] that azithromycin might be a facilitating factor to develop ABPA could not be supported.

After the index year, patients with ABPA had significantly lower cumulative FVC and FEV_1 values, significantly more hospitalization days, and increased need for IV antibiotic therapy compared to the control population, suggesting more severe disease and probably increased bronchial damage. Comparing the period before and after the index years, patients with ABPA showed significantly more hospitalization days and more IV antibiotic days but no significant differences in FEV_1 and FVC. This was not found in the control population (data not shown). These findings suggest that patients with ABPA can control a decrease in lung function and increase in bronchial damage by more intensive treatment with increased use

TABLE 6 Cumulative number of patients on treatment with the respective drugs during the pre-index period

Characteristic	Period	Category	Total	Proportion % (n)	*P*-value of chi-square
Inhaled corticosteroids	Pre-index	Controls	574	28.0 (161)	<0.0001*
	Pre-index	Cases	224	49.6 (111)	
Systemic corticosteroids	Pre-index	Controls	574	0.3 (2)	1.0000*
	Pre-index	Cases	224	0.0 (0)	
rhDNase	Pre-index	Controls	574	39.0 (224)	0.0180
	Pre-index	Cases	224	48.2 (108)	
Azithromycin	Pre-index	Controls	574	3.0 (17)	0.1042
	Pre-index	Cases	224	5.4 (12)	
Inhaled antibiotics	Pre-index	Controls	574	1.6 (9)	0.2978*
	Pre-index	Cases	224	0.4 (1)	

**P*-value of Fisher's exact (2-tail) test.

TABLE 7 Number of patients on treatment with the respective drugs during the post-index compared to the pre-index period in ABPA patients

Variable	Period	n	Proportion % (n)	*P*-value of chi-square test
Inhaled corticosteroids	Pre-index	168	56.5 (95)	0.0003
	Post-index	361	72.3 (261)	
Systemic corticosteroids	Pre-index	168	0.6 (1)	<0.0001*
	Post-index	361	11.6 (42)	
rhDNase	Pre-index	168	67.3 (113)	0.6003
	Post-index	361	69.5 (251)	
Azithromycin	Pre-index	168	18.5 (31)	0.1464
	Post-index	361	24.1 (87)	
Inhaled antibiotics	Pre-index	168	61.3 (103)	0.0109
	Post-index	361	73.1 (264)	

**P*-value of Fisher's exact (2-tail) test.

of IV antibiotics and more hospitalization days. This finding is not surprising, as Amin et al[4] reported that *Af* colonization and sensitization are already an independent risk factor for hospitalization. This result does not fit the data reported by Kraemer et al, who reported a faster decline in FEV_1 and FEF_{50} and increase in hyperinflation and ventilation inhomogeneity in ABPA patients compared to controls; they studied a mixed population of *Pa*-negative and *Pa*-colonized patients.

Our results corroborate with the data of Kaditis et al; they reported, in a European register-based study, no significant effect on lung function decline after ABPA in *Pa*-negative and *Pa*-colonized children and adolescents. This study did not look at treatment data.

After the index year, a significantly increased use of inhaled antibiotics was observed in patients with ABPA. This is an unexpected finding because in Belgium, inhaled antibiotics can only be started with an FEV1 less than or equal to 75% in *Pa*-colonized patients. This could be explained due to of label use in clinical deterioration.

As expected, more patients were on oral corticosteroids, which is the first-line drug for ABPA treatment.

A weakness of this study relies on the fact that retrospective data of the Belgian CF register were studied. The impact of treatment changes or complications (eg, pneumothorax, hemoptysis) during the study period are not considered. Therefore, cautious interpretation is mandatory and these findings need to be confirmed. Double-blind placebo-controlled prospective studies are difficult to implement because the incidence of ABPA is low and it is not ethical to withheld CF patients from active treatment.

5 | CONCLUSIONS

In *Pa*-negative patients, a lower FEV1 value is seen in the year of diagnosis. No arguments for more pronounced bronchial damage as a facilitating factor were documented. During the 5-year period after diagnosis of ABPA, patients have, relying on lung function data, more bronchial damage and need a more intensive treatment compared to the control group. After the year of diagnosis, ABPA patients could stabilize bronchial damage measured by lung function, with a more intensive treatment regimen. A higher use of inhaled steroids and rhDNase was recorded in the pre-index years, suggesting a possible impact; further research should try to clarify any causality.

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How to cite this article: De Baets F, De Keyzer L, Van daele S, et al. Risk factors and impact of allergic bronchopulmonary aspergillosis in *Pseudomonas aeruginosa*-negative CF patients. *Pediatr Allergy Immunol*. 2018;00:1–6. https://doi.org/10.1111/pai.12953