ORIGINAL ARTICLE AIRWAY DISEASES

Aspergillus sensitization is associated with airflow limitation and bronchiectasis in severe asthma

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Abstract

Background: Abnormalities, including bronchiectasis, that are detectable on high-resolution computed tomography (HRCT) have been associated with severe asthma. Bronchiectasis is associated with the diagnosis of allergic bronchopulmonary aspergillosis (ABPA), which also occurs in patients with severe asthma. We sought to determine the frequency and pattern of HRCT abnormality and the relationship with *Aspergillus fumigatus* sensitization in one severe asthma population.

Methods: We examined our database of patients attending a supraregional severe asthma service (Manchester, UK). Clinical, physiological and immunological characteristics were compared between those with HRCT evidence of airway disease (specifically bronchiectasis) and those with no radiological abnormality.

Results: Of 133 patients analysed, 111 (83.4%) had an abnormal HRCT with bronchial wall thickening (41.3%), bronchiectasis (35.3%), air trapping (20.3%) and bronchial dilatation (16.5%) occurring most frequently. Radiological evidence of airway disease was associated with more obstructive spirometry (postbronchodilator FEV_1/FVC ratio 73.2% *vs* 64.8% [difference −8.5%, 95% CI −16.9 to −0.1, $P = 0.048$]). *A. fumigatus* sensitization was associated with a 2.01 increased hazard ratio of bronchiectasis (95% CI 1.26 to 3.22, $P = 0.005$), and more obstructive spirometry (postbronchodilator FEV_1/FVC ratio 57.6 *vs* 70.3 [difference −12.8, 95% CI −19.8 to −5.7, $P = 0.001$]). Patients with *A. fumigatus* sensitization had variable clinical and radiological characteristics that frequently did not conform to the conventional diagnostic criteria for ABPA.

Conclusion: Patients with severe asthma frequently have radiological abnormalities on HRCT. Sensitization to *A. fumigatus* is associated with bronchiectasis and greater airflow obstruction, even when diagnostic criteria for ABPA are not met.

Patients with severe asthma frequently have macroscopic anatomical abnormalities secondary to airway remodelling that are detectable with high-resolution computed tomography (HRCT) (1–5). Compared with healthy volunteers, patients with asthma have increased bronchial wall thickening on HRCT, and disease severity is a surrogate for demonstrable structural airway change (1, 2, 6–8). Bronchial wall thickening, luminal narrowing and air trapping seen on HRCT have been shown to correlate with airflow limitation, neutrophilic airway inflammation, bronchial epithelial thickness at biopsy, and also bronchodilator response in patients with severe asthma (1, 2, 8, 9). Other radiological features associated with severe asthma include mucus impaction, bronchial dilatation and bronchiectasis (6, 9–12). Despite these observations, the relative frequency of radiological abnormality in the severe asthma population is not well characterized, and the clinical implications of finding airway disease on HRCT are not yet fully defined.

Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with pre-existing lung disease and is characterized by a predominately Th2-mediated allergic response to *Aspergillus* colonizing the host airway (13). This leads to worsening of the underlying lung condition, and as such patients with ABPA are over-represented in the severe asthma population. Published case series estimates that 0.7–3.5% of the referred asthma population have ABPA, with the prevalence increasing to between 5% and 25% of patients regularly attending asthma clinics (13–20). In the asthma population, diagnostic

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criteria for ABPA include immediate cutaneous hyperreactivity to *Aspergillus* antigen, circulating immunoglobulin E (IgE) >1000 KIU/l and raised *Aspergillus*-specific IgE and/or IgG (21, 22). Further pointers to the diagnosis include expectoration of mucus plugs, positive identification of *Aspergillus* species in respiratory samples, elevated serum IgG precipitins and a positive delayed cutaneous hypersensitivity response. These criteria were first proposed in 1977 and codified later, but there is a considerable ongoing debate about the relative merits of the radiological, microbiological and immunological tests utilized, and how to best differentiate *Aspergillus* sensitization, *Aspergillus* colonization and ABPA as clinical entities (13, 16, 23). In particular, the precise cut-off value for total IgE and the method by which to demonstrate *Aspergillus* sensitization (cutaneous hyperreactivity or specific IgE) has been questioned. Division of ABPA into disease associated with central bronchiectasis (ABPA-CB) and that with serological evidence of sensitization only (ABPA-S) is also described (13, 16).

Our centre has recently recommended defining another category of patients labelled severe asthma with fungal sensitization (SAFS) (24). We postulated that these patients represent a group of severe asthmatics with circulating IgE and airway colonization by *Aspergillus* or other fungi at lower concentrations than that seen in ABPA. The resulting allergic response may be clinically important but below the arbitrary threshold for diagnosis of ABPA. Observational data demonstrate colonization of airways by *Aspergillus fumigatus* in patients with severe asthma is more frequent in patients with concomitant evidence of systemic sensitization and is also associated with bronchiectasis and greater impairment of lung function (25). Identification of such patients is also of value as a recent randomized placebo-controlled trial has shown clinical benefit in asthma outcomes in patients with SAFS treated for long periods with antifungal drugs (26).

We sought to determine the frequency of macroscopic airway abnormality on HRCT in our severe asthma population. In addition, we have examined the related features of bronchiectasis in association with severe asthma and associations between this radiological characteristic and *A. fumigatus* sensitization.

Methods

Patients

Information about patients attending the Manchester severe asthma service is currently entered into a database, some of which is centrally collated along with that from other centres across the UK and forms part of a larger ongoing networked study (27). Patients are included in the Manchester database if they are >16 years, attend the supraregional dedicated severe asthma clinic and have given informed consent. For this study, we examined the Manchester severe asthma database of for patients in whom an HRCT scan had been performed, and the full report was available. Ethical approval was not required for this analysis.

CT scan reporting

High-resolution computed tomography images of all patients attending the severe asthma clinic are routinely reviewed for the following specific features of airway disease: bronchial wall thickening, bronchial dilatation, central bronchiectasis, peripheral bronchiectasis, air trapping, mucus plugging and ground-glass attenuation. A standard HRCT protocol is employed by our radiology department using a 16-slice Siemens scanner with 5-mm collimation and a scan time of 0.5 s per slice; the intra-operator reproducibility of HRCT reporting in patients with severe asthma within our department has previously been estimated as 95% (unpublished data).

Aspergillus sensitization and colonization

Allergic bronchopulmonary aspergillosis was defined as asthma, a total serum IgE >1000 KIU/l and an elevated *A. fumigatus*-specific IgE, which we use in lieu of immediate cutaneous hypersensitivity response to *Aspergillus*; subdivision into disease with and without the evidence of central bronchiectasis was then based on the associated HRCT report. Sensitization to *A. fumigatus* was defined as an elevated total and *A. fumigatus*-specific IgE but without the other features necessary for a diagnosis of ABPA. Patients were considered to have airway colonization if *Aspergillus* species were positively identified on direct staining and microscopy or growth in fungal media. Growth or sensitization to species other than *A. fumigatus* was not considered in this study. All microbiology samples were processed according to BSOP57, with the modification that 10 μl of processed sample was plated instead of 1 μl (28).

Statistical analysis

SPSS version 19 (SPSS Inc, Chicago, IL, USA) for Macintosh and PRISM Version 4 (GraphPad Software Inc, La Jolla, CA, USA) for Macintosh were used to perform the analysis. Data were examined for normality using distribution plots and the Shapiro–Wilk test; non-Gaussian data (IgE and peripheral eosinophil count) were log transformed prior to analysis. Mean values and proportions between groups were compared using the unpaired Student's *t*-test and Fisher's exact test, respectively. Associations between variable were determined using Pearson's correlation. Differences were considered significant at $P \leq 0.05$ (two-tailed).

Results

Data for 179 patients are currently entered in the Manchester severe asthma database of which 133 underwent HRCT and had the full report available. All patients met the American Thoracic Society criteria for refractory asthma (Table 1) (29). The majority of patients (n = 111, 83.4%) had features on HRCT consistent with airway disease, and 47 patients (35.3%) had evidence of bronchiectasis (Table 2). Similar numbers of those with bronchiectasis had a central (n = 21) or peripheral (n = 26) distribution of disease. In patients

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Table 1 Patient characteristics

Characteristic	Value
Age – years	47.2 (1.2)
Male/Female – *n*	42/91
Atopic/Nonatopic – *n*	62/71
Disease duration – years	27.5 (1.5)
Postbronchodilator FEV_1 – % predicted	75.3 (2.7)
Postbronchodilator FEV_1/FVC ratio	65.9 (1.7)
ICS dose – μg BDP equivalent*	1800 (1000–2000)
Maintenance oral steroids – *n*	12

BDP, beclometasone diproprionate; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity.
All values expressed as mean (standard error of mean) except: *median (interquartile range).

Table 2 Frequency of abnormal findings on thoracic high-resolution computed tomography in patients with severe asthma

Findings on CT, *n* = 133	*n* (%)
Normal	22 (16.5)
Bronchiectasis	
Any	47 (35.3)
Central	21 (15.8)
Peripheral	26 (19.5)
Airway disease (no bronchiectasis)	
Any	62 (46.6)
Bronchial wall thickening	55 (41.3)
Bronchial dilatation	22 (16.5)
Air trapping	27 (20.3)
Mucus plugging	15 (11.3)
Ground-glass changes only	2 (1.5)

Numbers do not add up as some patients had more than one abnormal feature.

without bronchiectasis, the most common abnormality was bronchial wall thickening and bronchial dilatation. In a number of patients (26), clinically important unexpected radiological abnormalities were also detected including (*n*) the following: pulmonary nodules (4), consolidation (4), atelectasis and scarring (8), emphysema (3), parenchymal sarcoid (1), tracheomalacia (1), parenchymal cysts (1), adenopathy (3) and features of pulmonary hypertension (1).

Excluding those with bronchiectasis, severe asthma patients with radiological features of airway disease on HRCT had more obstructive pre- and postbronchodilator spirometry than those in which radiological abnormalities were absent (Table 3). There were no other differences between these groups including age, disease duration, circulating IgE level or *A. fumigatus* sensitization. In contrast, patients with severe asthma and concomitant bronchiectasis had less response to inhaled bronchodilator (mean difference −6.0 ml [95% CI −10.9 to −1.1, $P = 0.017$]), and there was a trend towards longer disease duration (mean difference −6.1 years [95% CI −12.3 to 0.1, $P = 0.055$]) than those severe asthmatics without bronchiectasis (Table 4). *A. fumigatus* sensitization occurred frequently (36.2% of those tested) and was associated with a 2.01-fold (95% CI 1.26 to 3.22, $P = 0.005$) increased risk of having bronchiectasis in our severe asthma population. The pre- and postbronchodilator FEV_1/FVC ratio (SEM) in patients sensitized to *A. fumigatus* was 54.0 (2.3) and 57.6 (2.4) compared with 68.0 (1.8) and 70.3 (2.3) in those without evidence of sensitization, giving a mean difference of −13.9 (95% CI −19.7 to −8.1, $P < 0.001$) and −12.8 (95% CI −19.8 to −5.7, $P = 0.001$), respectively. Although the pre- and postbronchodilator FEV_1 was also lower in those sensitized to *A. fumigatus* compared to those without sensitization (61.7% predicted *vs* 70.5% predicted, and 69.9% predicted *vs* 80.1% predicted), the difference between the means failed to reach statistical significance ($P = 0.108$ and $P = 0.082$, respectively).

Details of the patients with *Aspergillus* sensitization (including ABPA) and bronchiectasis are summarized in Table 5. Seven of the 22 patients with bronchiectasis (31.8%) met the conventional criteria for ABPA, but only three had central bronchiectasis, and the remainder had a peripheral distribution of airway disease. Although the remaining *Aspergillus*-sensitized patients also had severe asthma and bronchiectasis (often associated with fungal colonization, significantly elevated *Aspergillus* IgE or marked peripheral eosinophila), the total IgE precluded a diagnosis of ABPA. The overall prevalence of ABPA in our severe asthma population was 13/133 (9.0%), which included five patients with no evidence of bronchiectasis in any distribution. There was no association between the degree of *A. fumigatus* sensitization (*Aspergillus*-specific IgE) and any other marker of disease severity or indeed total circulating IgE (Fig. 1).

Discussion

Study limitations

Our study has a number of possible shortcomings. This is a group of patients attending a single severe asthma centre. Respiratory specialists referred the patients who had already been established on a variety of anti-asthma treatments that would influence some of the measured variables (e.g. lung function and blood eosinophilia). There may also be a degree of referral bias that is difficult to quantify, as local respiratory physicians would be aware of the research and clinical activity at our centre. We have used peripheral blood *A. fumigatus*-specific IgE only as a marker of sensitization, but not other immunological techniques or the cutaneous hypersensitivity response. Opinion is conflicting as to the utility of each of these indices for determining sensitization, and published evidence suggests a degree of discordance exists between different surrogate measures (30, 31). Until recently, our current practice was only to test for *Aspergillus*-specific IgE in the majority of cases, and the retrospective nature of this study precluded acquisition of information about the cutaneous response to allergen. It is possible that we have underestimated the prevalence of *Aspergillus* sensitization or

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Table 3 Comparison of severe asthma patients with and without features of airway disease on high-resolution computed tomography

Characteristic	Normal CT (n = 22)	Features of airway disease on CT (n = 62)	Difference (95% CI)	P value
Age – years	44.5 (3.5)	46.9 (1.4)	−2.3 (−8.7 to 4.0)	0.467
Disease duration – years	23.7 (3.5)	25.5 (2.2)	−1.8 (−10.2 to 6.5)	0.685
Pre-BD FEV_1 – % predicted	71.1 (6.7)	63.3 (2.4)	−7.8 (−20.0 to 4.4)	0.213
Pre-BD FEV_1/FVC ratio	70.9 (2.9)	60.9 (1.3)	−10.1 (−16.6 to −3.5)	0.003
Post-BD FEV_1 – % predicted	83.2 (6.6)	74.7 (2.2)	−8.5 (−21.5 to 4.6)	0.201
Post-BD FEV_1/FVC ratio	73.2 (3.4)	64.8 (1.5)	−8.5 (−16.9 to −0.1)	0.048
BD response –% FEV_1	16.6 (3.5)	13.5 (2.2)	−3.1 (−9.5 to 3.4)	0.343
Residual volume – % predicted	118.9 (8.8)	125.1 (3.7)	6.1 (−14.9 to 27.2)	0.564
Total lung capacity – % predicted	103.1 (3.2)	100.2 (1.5)	−2.9 (−11.0 to 5.2)	0.478
Peripheral eosinophils × 10^9/l*	0.14 (0.11–0.19)	0.19 (0.16–0.23)	0.76 (0.38–1.54)	0.444
Total IgE – KIU/l*	123 (79–191)	195 (158–239)	0.62 (0.27–1.46)	0.269
Nasal Polyps – n (%)†	6/22 (27.2)	8/51 (13.6)	0.50 (0.20–1.27)	0.188
Aspergillus sensitization – n (%)†	6/21 (28.6)	14/52 (26.9)	0.94 (0.42–2.12)	>0.99

BD, bronchodilator; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; KIU/l, thousand international units per litre; IgE, immunoglobulin E.

All data as mean (standard error of mean) except:

*Geometric mean (standard error geometric mean) and difference expressed as fold change.

†Ratio (percentage) and difference expressed as hazards ratio.

Table 4 Comparison of severe asthma patients with and without bronchiectasis on high-resolution computed tomography

Characteristic	No bronchiectasis (n = 86)	Bronchiectasis (n = 47)	Difference (95% CI)	P value
Age – years	46.3 (1.4)	50.0 (2.0)	−3.7 (−8.4 to 0.9)	0.119
Disease duration – years	25.4 (1.8)	31.5 (2.7)	−6.1 (−12.3 to 0.1)	0.055
Pre-BD FEV_1 – % predicted	64.3 (4.5)	67.7 (4.5)	−3.3 (−13.5 to 7.2)	0.536
Pre-BD FEV_1/FVC ratio	63.5 (1.6)	63.0 (2.6)	0.5 (−5.2 to 6.2)	0.871
Post-BD FEV_1 – % predicted	76.8 (2.8)	74.7 (5.6)	2.0 (−9.3 to 13.3)	0.723
Post-BD FEV_1/FVC ratio	66.7 (1.8)	64.0 (4.0)	2.6 (−4.6 to 9.8)	0.472
BD response –% FEV_1	14.2 (1.4)	8.2 (1.7)	−6.0 (−10.9 to −1.1)	0.017
Residual volume – % predicted	124.0 (4.4)	110.9 (5.3)	13.2 (−0.7 to 27.0)	0.062
Total lung capacity – % predicted	100.9 (1.7)	97.3 (2.4)	3.6 (−2.2 to 9.4)	0.219
Peripheral eosinophils × 10^9/l*	0.23 (0.19–0.29)	0.17 (0.15–0.20)	0.73 (0.45–1.18)	0.198
Total IgE – KIU/l*	166 (138–200)	229 (173–302)	0.72 (0.38–1.38)	0.328
Nasal Polyps – n (%)†	15/82 (9.8)	7/43 (16.3)	1.8 (0.6–5.35)	0.583
Aspergillus sensitization – n (%)†	20/75 (26.7)	22/41 (53.7)	2.01 (1.26 to 3.22)	0.005

BD, bronchodilator; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; KIU/l, thousand international units per litre; IgE, immunoglobulin E.

All data as mean (standard error of mean) except:

*Geometric mean (standard error geometric mean) and difference expressed as fold change.

†Ratio (percentage) and difference expressed as hazards ratio.

ABPA as a result. The HRCT scans had not all been reported by a single radiologist, and interpretation of the scans has been restricted to extraction of specific information against standardized criteria from the radiologist's report. While potentially introducing a degree of error related to interoperator variability, this approach has been adopted to enable uniformity of data interpretation.

Some information that is necessary to fully characterize the patients with respect to *Aspergillus* was absent (e.g. not every patient had respiratory samples cultured *Aspergillus* spp. or underwent testing for *Aspergillus* precipitins). This reflects varying practice among our clinicians and also how easy it was for patients to expectorate in clinic, and in this regard highlights the disparity in opinion about the relative significance of markers used for the evaluation of patients with *Aspergillus* sensitization and possible ABPA. For the purpose of this analysis, we have not considered potential concomitant sensitization to other fungal allergens (largely as numbers would be too small to derive any meaningful interpretation), which may be important, although we have described the presence of such sensitization within this population previously (24, 26).

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Table 5 Characteristic features of patients with bronchiectasis and Aspergillus sensitization

Gender/ age (years)	Second line therapy (mg/day)	FEV_1 (% predicted)	Eosinophil count ($\times 10^9$/l)	Total IgE (KIU/l)	Aspergillus-specific IgE (KIU/l)	Aspergillus precipitants	Aspergillus colonization	Pattern of bronchiectasis	Meets criteria for ABPA
F/58	I	82	0.37	3200	3.5	Negative	Positive (sputum)	Lower lobe Central	Yes (CB)
M/60	I	43	0.61	2800	23.7	Negative	Negative (sputum)	Multilobed Central	Yes (CB)
M/58	I	53	1.28	1600	1.4	Negative	Negative (sputum/BAL)	Multilobed Peripheral	Yes (S)
M/60	I	50	0.34	2900	11.2	Positive	Negative (Sputum)	Multilobed Peripheral	Yes (S)
F/40	P (30) I	29	0.28	1100	2.0	Not available	Unknown	Multilobar Central	Yes (CB)
M/57	I	78	1.04	1500	16.5	Positive	Positive (Sputum)	Upper lobe Peripheral	Yes (S)
F/52	P (10) I	45	0.51	4800	48.6	Negative	Unknown	Lower lobe Peripheral	Yes (S)
M/43	P (35) I	50	0.15	230	0.5	Not available	Unknown	Upper lobe Peripheral	No
F/67	I	78	0.88	990	18.4	Negative	Unknown	Upper lobe Peripheral	No
F/43	I	72	0.51	490	13.5	Positive	Unknown	Diffuse Peripheral	No
M/54	Nil	100	0.46	150	50.0	Negative	Negative (sputum)	Multilobed Central	No
F/43	I	80	0.70	700	0.5	Positive	Negative (Sputum)	Upper lobe Peripheral	No
M/55	P (30)	31	0.25	110	8.0	Not available	Unknown	Multilobed Central	No
M/65	P (10)	46	0.42	540	8.7	Not available	Unknown	Multilobed Peripheral	No
M/58	Nil	39	0.28	260	2.8	Not available	Unknown	Lower lobe Peripheral	No
M/38	I	69	1.03	55	0.8	Not available	Unknown	Multilobar Peripheral	No
F/59	I	70	0.71	296	20.8	Negative	Negative (Sputum)	Lower lobe Peripheral	No
F/44	P (5)	74	0.75	260	3.4	Not available	Negative (Sputum)	Upper lobe Peripheral	No
M/42	Nil	29	0.55	87	1.2	Negative	Positive (BAL)	Multilobar Central	No
F/18	Nil	112	0.18	400	3.5	Not available	Unknown	Multilobar Central	No
M/40	I	106	1.19	230	0.6	Not available	Unknown	Multilobar Central	No
F/89	Nil	104	0.13	220	0.9	Not available	Unknown	Multilobar Central	No

ABPA, allergic bronchopulmonary aspergillosis; BDP, beclometasone diproprionate; CB, central bronchiectasis; F, female; FEV_1, forced expiratory volume in first second; ICS, inhaled corticosteroids; I, itraconazole; IgE, immunoglobulin E; IgG, immunoglobulin G; KIU/l, thousand international units per litre; M, male; P, prednisilone; S, serology; IgE, immunoglobulin E.

HRCT abnormalities and *Aspergillus* sensitization

The majority of our patients had an abnormal HRCT and radiological evidence of airway disease on HRCT translated into a greater degree of airflow limitation, which is consistent with findings from other similar studies (2, 9, 11). This appears biologically plausible as asthma-related pathological change in the airways (mucus hypersecretion, increased bronchial wall thickening, and increased bronchial tone) proportionate to disease severity could conceivably lead to macroscopic change and more profound airflow limitation. Imaging and lung function appear to be alternate-modality surrogates of this same process.

Although an association between bronchiectasis and asthma has been noted previously, this relationship has infrequently been examined specifically in the severe asthma population or in relation to other disease characteristics particularly *Aspergillus* sensitization. The frequency of bronchiectasis (35.3%) and *Aspergillus* sensitization (36.2%) in our severe asthma population is comparable with that reported elsewhere (10, 14, 32). It is impossible to determine the mechanism that underpins bronchiectasis in asthma or to ascribe causality based on the current retrospective observational data; however, it is noteworthy that *A. fumigatus* sensitization was a statistically significant risk factor for this complication but not for other features of asthma-related radiological abnormality (Tables 3 and 4). Fairs et al. (25) recently reported data from 79 prospectively recruited patients with asthma attending another UK asthma clinic (the majority of which had severe disease) and showed a significant reduction in postbronchodilator FEV_1 in those patients with *Aspergillus* sensitization (68% predicted *vs* 88%), which is comparable with the values obtained from our patients (69.9% predicted and 80.1% predicted, respectively). In the same study, the frequency of bronchiectasis was approximately twofold higher in patients with *Aspergillus* sensitization (68% *vs* 35%), which is also comparable with our data (53.7% *vs* 26.7%).

In our population of severe asthmatics with associated *A. fumigatus* sensitization, the pattern of bronchiectasis was manifest with a high degree of variability: peripheral, central, localized and multifocal changes were noted (Table 5). There was also variability in other markers traditionally regarded as important when considering a diagnosis of ABPA, in particular peripheral eosinophil count, total IgE and positive microbiological identification. As such, this process is likely to represent a continuum, with *Aspergillus* sensitization leading to progressive allergic airway inflammation, remodelling and ultimately bronchiectasis. It remains unclear whether there are factors that may predetermine or increase the risk of certain individuals becoming sensitized to *Aspergillus* to begin with and how that sensitization will be expressed as

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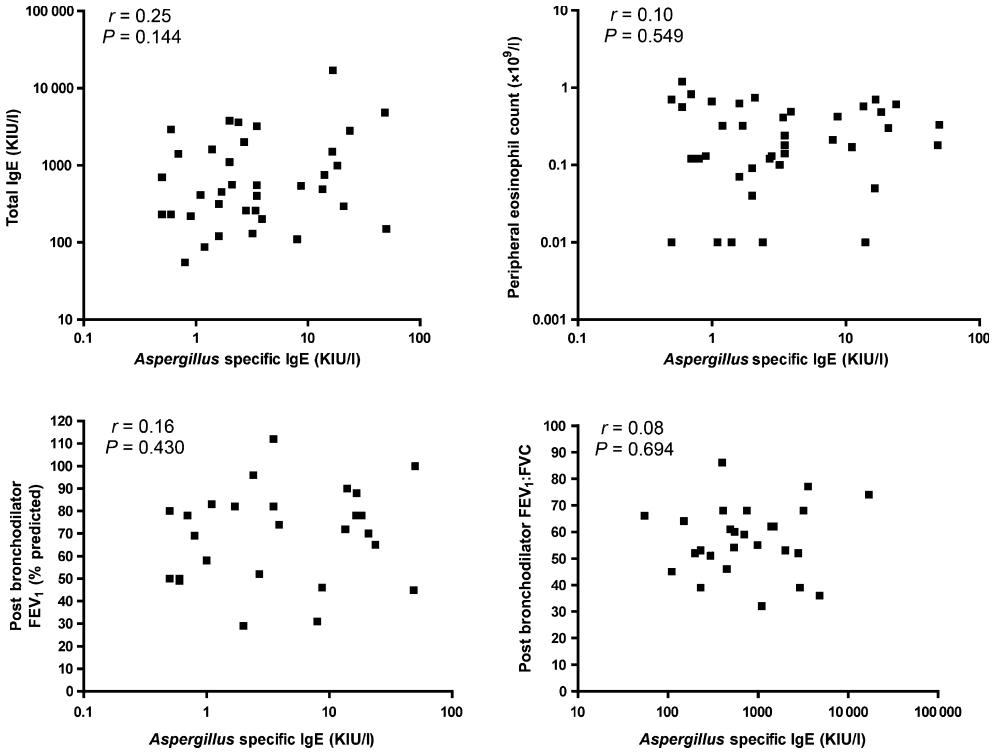

Figure 1 Lack of correlation between Aspergillus sensitization and alternative surrogate markers of disease severity in patients with severe asthma. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; KIU/l, thousand international units per litre.

either altered asthma severity or macroscopic airway damage. There appears to be a disconnect between the degree of allergic sensitization (i.e. *Aspergillus*-specific IgE) and other markers of disease severity, specifically spirometric indices, total IgE, radiological abnormality and eosinophil count (Fig. 1 and Table 5). Possible mechanisms for this include a differential response to concomitant asthma therapy, variable host immunity and a potential interaction between other aspects of pre-existing airway disease (e.g. co-sensitization to alternate allergens or fungi) (33). Measuring *A. fumigatus*-specific IgE only quantifies one part of the exaggerated host response to fungal colonization and does not take account of any direct injury caused by this airborne fungus, cell-mediated immunity or the airway eosinophil tracking, which characterizes ABPA. Given that fundamental aspects of this complex interaction are missing from the way we describe and label *Aspergillus* sensitization in the asthma population, the lack of association between surrogate markers is therefore unsurprising. This study supports the growing body of evidence that clinical manifestations of airway disease, host response to *Aspergillus* colonization, airway remodelling and the effect of therapeutic intervention is a highly heterogeneous and continuous process. Diagnostic subdivision of asthma associated with *Aspergillus* into sensitization, ABPA-S and ABPA-CB appears arbitrary and fails to encapsulate this phenomenon in a biologically complete or clinically applicable way.

Conclusion

The majority of patients with severe asthma have features of airway disease on HRCT, which in turn is associated with more obstructive spirometry. Bronchiectasis also occurs frequently in this group of patients, and *Aspergillus* sensitization is associated with an increased risk for this complication. There is a high degree of immunological, radiological and physiological variability among patients with severe asthma, bronchiectasis and *Aspergillus* sensitization. Defining ABPA based on the established historical criteria may therefore be unhelpful. In patients with severe asthma, clinicians should retain a low threshold for undertaking HRCT specifically to look for evidence of bronchiectasis, particularly in those sensitized to *Aspergillus*.

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Conflict of interest

No author has any conflict of interest to declare.

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