

Allergic Bronchopulmonary Aspergillosis in the Asthma Clinic*

A Prospective Evaluation of CT in the Diagnostic Algorithm

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Objective: Allergic bronchopulmonary aspergillosis (ABPA) occurs in cases of atopic asthma and may result in important lung disease. Early diagnosis is essential as this disease is responsive to steroids. However, while asthma is common, ABPA is infrequently diagnosed. CT allows precision in the diagnosis of central bronchiectasis (which is virtually pathognomonic of ABPA) and may enable earlier diagnosis.

Design: A prospective evaluation of 255 patients with asthma for ABPA, using skin prick testing (SPT) for *Aspergillus fumigatus* (AF) as a screening tool and incorporating CT into the diagnostic algorithm.

Setting: Asthma clinic, Green Lane Hospital, Auckland, New Zealand.

Participants: Patients with asthma.

Interventions: ABPA was diagnosed using "essential" criteria (*ie*, asthma, SPT positivity to AF, elevated serum total IgE, elevated serum AF-specific IgE, and pulmonary infiltrates seen on chest radiography or central bronchiectasis seen on CT scan) and "minimal essential" criteria (*ie*, asthma, SPT positivity, and central bronchiectasis).

Measurements and results: Two hundred fifty-five consecutive patients with asthma who consented to SPT were studied: 218 of 255 patients (86.8%) were atopic; and 47 of 255 patients (21.6%) were AF-positive, of whom 35 accepted further evaluation including CT scanning. A secure diagnosis of ABPA, satisfying all essential criteria, was evident in 9 of 35 patients (25.7%), a proportion that increased to 13 of 35 patients (37.1%) by using the minimal essential diagnostic criteria.

Conclusions: SPT positivity to AF was present in approximately 20% of patients in the asthma clinic. A diagnosis of ABPA is disclosed by CT in 25 to 40% of SPT-positive patients, depending on the selection of diagnostic criteria. These findings support the use of SPT as a screening tool in the asthma clinic and indicate that a routine CT scan is warranted in SPT-positive patients.

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Key words: allergic bronchopulmonary aspergillosis; asthma; CT; skin prick testing

Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; AF = *Aspergillus fumigatus*; SPT = skin prick test

Allergic bronchopulmonary aspergillosis (ABPA) is associated with hypersensitivity to *Aspergillus fumigatus* (AF), occurring most commonly in atopic patients with asthma and sometimes resulting in severe lung damage. As corticosteroid therapy may prevent progression of the disease, early diagnosis is

essential. However, while asthma is a common diagnosis, ABPA is diagnosed infrequently, with the exact prevalence remaining uncertain. Skin prick testing

For editorial comment see page 7

for AF has been advocated strongly as a screening tool,¹⁻³ with a negative result effectively excluding ABPA.

The few published studies evaluating the prevalence of ABPA have been hampered by diagnostic imprecision. Essential diagnostic criteria include asthma, skin prick test (SPT) positivity to AF, elevated levels of serum total IgE, elevated levels of

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serum AF-specific IgE, and either a history of pulmonary infiltrates on chest radiography or central bronchiectasis.^{2,4,5} Central bronchiectasis is viewed as virtually pathognomonic of ABPA, provided that cystic fibrosis has been excluded as a diagnosis.^{2,6,7} However, chest radiography is neither sensitive nor specific.^{6,8} High-resolution CT allows precision in the definition of central bronchiectasis⁸⁻¹¹ with acceptable interobserver agreement.^{12,13} A diagnosis of ABPA then may be secured, possibly at an earlier stage. Indeed, the use of "minimal essential" criteria (*ie*, asthma, SPT positivity for AF, and central bronchiectasis) has been proposed.² The other two "minimal essential" criteria (*ie*, asthma and SPT positivity for AF) might logically be used to select patients to undergo CT scanning. Thus far, CT studies have been retrospective, comparing morphologic features in previously diagnosed cases of ABPA to those in asthmatic patients who are SPT-positive for AF.^{9,10}

We aimed to evaluate prospectively the prevalence of ABPA in an asthma clinic, using the SPT for AF as a screening tool and incorporating CT scanning in the diagnostic algorithm. The clinical utility of CT scanning then was examined. Clinical and investigative features reported retrospectively in ABPA^{5,14,15} were compared with an historical group of patients with asthma who had ABPA and a randomly selected group of atopic patients with asthma who were SPT-negative for AF.

MATERIALS AND METHODS

Subjects

Approval was obtained from our local ethics committee. SPT was offered to all asthma patients attending the Green Lane Hospital outpatient asthma clinic over an 18-month period. Patients were recruited prospectively with written informed consent.

All asthma patients who proved to be SPT-positive for AF underwent a full evaluation for ABPA, including CT scans. A secure diagnosis of ABPA required satisfaction of all essential

diagnostic criteria (Table 1).^{2,4,5} Over the same period atopic patients with asthma who were SPT-negative for AF were randomly selected and underwent the same evaluation. Another group of asthma patients, previously diagnosed with ABPA, consented to reevaluation.

Asthma was diagnosed by American Thoracic Society criteria,¹⁶ with atopy defined as SPT positivity (mean wheal diameter, ≥ 3 mm) to one or more allergens. Exclusion criteria were a previous infection with *Mycobacterium tuberculosis*, systemic or local conditions known to predispose the patient to bronchiectasis (*ie*, immunodeficiency, cystic fibrosis [excluded by sweat testing], collagen vascular disease, inflammatory bowel disease, sarcoidosis, or inhaled foreign body), α_1 -antitrypsin deficiency, and pregnancy.

Data Collection

Demographic details, the duration and age of onset of asthma, the presence of allergic rhinitis, eczema, a family history of asthma (defined as positive if at least one first-degree relative, such as a parent, sibling, or child, had asthma), and a history of sputa plugs were obtained. Medication use was recorded. Asthma severity was assessed by the frequency of β_2 -agonist use, night waking, the need for continuous oral corticosteroids and oral corticosteroid courses in the last year, and emergency visits and hospital admissions for asthma.

FEV₁, FVC, and FEV₁/FVC ratio (V6200 Autobox D_L; SensorMedics; Yorba Linda, CA) were measured before and after the patient inhaled salbutamol, 400 μ g.

SPT was performed with the following eight common aeroallergens: AF, mixed *Aspergillus* species, privet, grass pollen mix, house dust mites, dog hair, cat fur, feather mix, and negative and positive controls (Hollister-Stier; Spokane, WA). After 15 min, the mean wheal diameter was measured. The patients had not been allowed to use antihistamines in the preceding 48 h.

Laboratory investigations included the following: total serum IgE measured by latex-enhanced nephelometry (Behring Diagnostics; Marburg, Germany); precipitating antibodies to AF; using unconcentrated serum by double-gel diffusion Ouchterlony assay (Mercia Diagnostics; Camberley, UK) and serum eosinophils. Serum levels of AF-specific IgE were determined using an enzyme-labeled immunoassay with a liquid-phase allergen (AlaSTAT; Diagnostic Products Corporation; CA), expressed semiquantitatively on a grade between 0 and 4+.

Radiology

CT scans and chest radiographs were evaluated independently by two observers, who had no knowledge of the findings from clinical evaluations or the results of laboratory investigations. Consensus agreement was reached when observers disagreed as to the presence or absence of individual abnormalities. The CT protocol consisted of 1-mm sections acquired at 10-mm intervals from the lung apices to the bases at end inspiration, and 1-mm sections acquired at 20-mm intervals at end expiration (ProSpeed SX Advantage; GE Medical Systems; Waukesha, WI). The presence or absence of central bronchiectasis was scored on the CT scan. Chest radiographic appearance was categorized as normal or as compatible with ABPA (*ie*, upper zone-predominant bronchiectasis, perihilar distortion, fibrosis, loss of volume, mucus plugging, atelectasis, consolidation, and infiltrates^{6,7}).

Statistical Analysis

The results are stated as median (range). Nonparametric analysis of variance (Kruskal-Wallis test) was used to assess

Table 1—Diagnostic Criteria for ABPA

Criteria
Essential
Asthma*
SPT positivity for AF*
Elevated serum total IgE > 1,000 ng/mL
Elevated serum AF-specific IgE
History of pulmonary infiltrates on chest radiograph
Central bronchiectasis on CT scan*
Minor supporting
Positive precipitins
Serum eosinophilia

*Minimal essential criteria.

differences across groups, and the Wilcoxon rank sum test was used for two sample comparisons. Proportions were examined using Fisher's Exact Test. A p value of < 0.05 was considered significant. Interobserver variation was quantified using the κ coefficient of agreement. Clinical predictors of ABPA were explored using logistic regression. All analyses were performed using computer software (Stata, version 5 for Windows; Stata Corp; College Station, TX).

RESULTS

Four hundred sixteen consecutive patients with asthma were seen, with 255 (61%) consenting to an SPT. Atopy was demonstrated in 218 of 255 patients (86.8%). Forty-seven patients (21.6%) were SPT-positive for AF, and 35 patients entered the study, 9 patients did not wish to participate, 2 were unavailable for follow-up, and 1 had a history of tuberculosis. Nine of these SPT-positive patients (25.7%) satisfied all the essential diagnostic criteria for ABPA (Table 2). Central bronchiectasis was seen on CT scans in eight of the patients, and the remaining patient had a history of pulmonary infiltrates. An additional four patients with central bronchiectasis satisfied the minimal essential criteria (*ie*, asthma, SPT positivity for AF, and central bronchiectasis) proposed by Schwartz and Greenberger.² Observer agreement was moderate to good (central bronchiectasis, $\kappa = 0.50$; chest radiographic appearances, $\kappa = 0.65$). A compatible chest radiograph abnormality was present in 8 of 9 patients in whom ABPA was securely diagnosed and in 9 of 13 patients satisfying the minimal essential criteria compared to 5 of 26 patients with asthma who were SPT-positive for AF who did not have ABPA ($p < 0.0001$ and $p = 0.004$, respectively).

Group characteristics are shown in Table 3, with

the prospectively recruited cases of ABPA similar in all respects to the historical ABPA cases. Age, sex, and measures of asthma severity were comparable. Patients with ABPA (historical control subjects and prospective recruits) had a longer duration of asthma ($p = 0.0001$) and a greater number of positive results of SPTs ($p = 0.0001$) and were more likely to have a history of oral corticosteroid dependency ($p < 0.0001$), eczema ($p = 0.01$), and sputa plugs ($p < 0.0001$).

An inspection of the diagnostic criteria (Table 4) shows that 8 of 31 atopic patients with asthma who were SPT-negative for AF (25.8%) had positive Aspergillus precipitins (despite the use of unconcentrated sera). A history of pulmonary infiltrates was more common in historical control subjects than in prospectively recruited patients with ABPA. The mean wheal diameter to AF was larger in asthma patients with ABPA than in those who were SPT-positive for AF and did not have ABPA ($p = 0.004$). When the historical and prospectively recruited patients with ABPA were combined, a mean wheal diameter in AF of > 4 mm correctly predicted 35 of 36 patients with ABPA (97.2%), whereas 12 of 26 patients without ABPA (46.2%) had a mean wheal diameter ≤ 4 mm. The level of AF-specific IgE proved a similarly robust predictor of ABPA ($p < 0.0005$). Clinical predictors of ABPA (*ie*, a history of sputa plugs, oral corticosteroid dependency, and eczema) were examined using logistic regression. Independent determinants were a history of sputa plugs ($p = 0.003$) and eczema ($p = 0.05$), however, when analysis was confined to the prospectively recruited cases, only eczema was a significant determinant ($p = 0.01$).

Diagnostic strategies were evaluated for accuracy

Table 2—Diagnostic Criteria of Prospectively Recruited Asthma Patients Who Are SPT-Positive for AF Who Satisfied All Essential Criteria for ABPA*

Age, yr	Sex	SPT AF, mm	AF-Specific IgE	IgE, ng/mL	Pulmonary Infiltrates	Central Bxs	Pptns	Eosinophils, cells/mm ³
53	M	8	3	12,991	—	+	0	0
44	M	6	3	1,471	—	+	1	550
65	M	5	4	38,616	+	—	0	540
33	F	5	4	1,236	—	+	0	550
65	F	4	4	17,352	—	+	2	90
48	M	9.5	3	4,697	—	+	0	370
45	F	9.5	4	1,414	+	+	1	950
50	F	9.5	4	10,450	—	+	6	640
42	M	16	4	2,186	—	+	0	120
53†	F	3	0	154	—	+	0	280
50†	F	5	0	110	—	+	2	200
59†	F	7	1	276	—	+	1	610
72†	F	3.5	2	530	—	+	0	140

*M = male; F = female; Bxs = bronchiectasis; Pptns = precipitins.

†Patient satisfies minimal essential criteria only.

Table 3—Clinical Features Compared Among Patient Subgroups*

Clinical Features	Asthma Patients			
	SPT+ AF With ABPA		SPT+ AF Without ABPA† (n = 26)	SPT- AF† (n = 31)
	Historical Control Subjects (n = 27)	Prospectively Recruited Patients (n = 9)		
Age, yr	51.0 (21–74)	48.0 (33–65)	43.0 (25–80)	46 (19–76)
Sex, % men	44.4	44.4	50.0	25.8
Duration of asthma, yr	44.0 (4–70)‡§	45.0 (32–58) ¶	28.5 (1–61)‡	23.0 (1–46)§¶
History of plugs, %	74.1‡§	44.4	23.1‡	6.5§
Night waking, nights/wk	0 (0–5)	0 (0–7)	0 (0–7)	0 (0–7)
Prednisone courses in the last year	2 (0–3)	2 (2–3)	2 (0–3)	2 (1–3)
Hospital admissions in the last year	0 (0–6)	0 (0–1)	0 (0–3)	0 (0–2)
History of oral corticosteroid dependency, %	59.2‡§	44.4	23.1‡¶	3.2§ ¶
Current acute oral corticosteroid use, %	18.5	11.1	15.4	12.9
FEV ₁ , % predicted	72 (13–121)	57 (35–77)	71 (29–119)	71 (37–120)
Positive SPTs, No.	4 (1–7)‡	7 (4–9)‡§	5 (1–8)§	4 (1–7)
Allergic rhinitis, %	53.9	88.9	42.3	67.7
Eczema, %	44.0	66.7‡§	19.2‡	19.4§
Family history of asthma, %	55.6	88.9	50.0	61.3

*Values given as median (range), unless otherwise indicated. + = positive; - = negative.

†Patients were prospectively recruited.

‡Indicates significance between historical control subjects who are SPT+ with ABPA and prospectively recruited SPT+ patients without ABPA.

§Indicates significance between historical control subjects who are SPT+ with ABPA and prospectively recruited SPT- patients.

||Indicates significance between prospectively recruited SPT+ patients with ABPA and SPT+ patients without ABPA.

¶Indicates significance between prospectively recruited SPT+ patients with ABPA and SPT- patients.

and cost (per case of ABPA diagnosed) (Table 5). If all asthma patients who were SPT-positive for AF were formally screened for ABPA, incorporating CT routinely into the diagnostic algorithm (which is viewed as the “gold standard”), a CT scan cost of \$1,944 per ABPA case was generated. However, when CT scanning was limited to patients with

positive clinical predictors (*ie*, sputa plugs, eczema, or a history of oral corticosteroid dependency), the correct identification of all nine securely diagnosed cases of ABPA was achieved at a CT scan cost of \$1,167 per case, which is a favorable comparison. Other approaches were investigated. If CT scans had been confined to those patients who had chest

Table 4—Investigative Features Compared Among Patient Subgroups*

Investigative Features	Asthma Patients			
	SPT+ AF With ABPA		SPT+ AF Without ABPA† (n = 26)	SPT- AF† (n = 31)
	Historical Control Subjects (n = 27)	Prospectively Recruited Patients (n = 9)		
Essential criteria				
Wheal diameter to AF, mm	7.0 (5.0–10.5)‡	8.0 (4.0–16.0)§	4.5 (2.0–7.0)‡§	0
AF-specific IgE				
Scale 0–4	4 (3–4)‡	4 (3–4)	0 (0–2)‡	0 (0–3)
Score > 2, %	100	100	0	3.2
Total IgE, ng/mL	1,721 (180–33,480)	4,697 (1,236–38,616)	280 (79–7,013)	334 (72–6,055)
History of pulmonary infiltrates, %	92.3	22.2	7.7	0
Central bronchiectasis, %	88.9	88.9	15.4	6.5
Minor supporting criteria				
Precipitins to AF, %	85.2	44.4	15.4	25.8
Eosinophils, cells/mm ³	320 (0–1,220)	540 (0–1,640)	155 (0–980)	200 (0–740)

*Values given as median (range), unless otherwise indicated. See Table 3 for abbreviations.

†Patients were prospectively recruited.

‡p < 0.0001 comparing control subjects with recruited patients in asthma SPT+ AF without ABPA group.

§p = 0.004 comparing recruited subjects with asthma SPT+ AF with ABPA and asthma SPT+ AF without ABPA groups.

||p < 0.001 comparing recruited patients in asthma SPT+ AF with ABPA and asthma SPT+ AF without ABPA groups.

Table 5—Diagnostic Strategies for ABPA Based on Current Standard Practice With Cost Analyses

Strategies	No. of CT Scans Saved (n = 35)	ABPA Diagnosis		CT Scan Cost*/Secure Case of ABPA, US\$
		Secure (n = 9)	Minimal Essential Criteria (n = 13)	
Proceed directly to CT scan	0	9; no missed cases	13	1,944
If mean wheal diameter from AF > 4 mm, proceed to CT scan	13	8; 1 missed case	10	1,375
If clinical predictors are positive, proceed to CT scan	14	9; no missed cases	11	1,167
If mean wheal diameter from AF > 4 mm and clinical predictors are positive, proceed to CT scan	20	8; 1 missed case	9	938
If chest radiograph is compatible with ABPA, proceed to CT scan	22	8; 1 missed case	9	813
If level of AF-specific IgE is strongly elevated (grade > 2), proceed to CT scan	25	9; no missed cases	9	556

*Radiology costs based on a cost for CT scan of \$500.

radiograph abnormalities that were compatible with ABPA, eight of nine secure cases of ABPA would have been diagnosed, at a cost of \$813. However, three of four cases satisfying the minimal essential criteria would have been missed. The cheapest, most accurate approach was to base CT performance on the strength of the serologic IgE response to AF. However, although secure ABPA was always diagnosed, none of the four patients with ABPA defined using the minimal essential criteria would have been detected.

DISCUSSION

An early diagnosis of ABPA is highly desirable, as corticosteroid therapy may prevent considerable lung damage.^{17,18} However, the correct choice of investigations in the construction of an efficient diagnostic algorithm depends on the following two factors: the prevalence of the disease, and the criteria used to make the diagnosis.

The present study confirms that the prevalence of ABPA in the asthma clinic is sufficiently high to justify the use of a protocol for diagnosis (including routine skin testing). The high prevalence of positivity to AF on skin testing (22%) is compatible with the 22 to 28% prevalence reported in other asthma clinic series.^{19,20} The diagnostic yield of CT scanning in unselected SPT-positive patients has not been evaluated previously, but it is unlikely that the frequency of ABPA at our center (25% or 37% of SPT-positive patients, depending on the choice of diagnostic criteria) differs materially from that in other asthma clinic populations. Thus, it can be argued that the prevalence of ABPA in a typical asthma clinic is likely to exceed 5%. Despite a higher than expected

prevalence in asthma clinics, ABPA continues to be diagnosed infrequently in routine respiratory practice. The underdiagnosis of ABPA can be ascribed, in part, to a lack of routine skin testing in most asthma clinics.¹⁻³ However, variations in diagnostic criteria between centers may be an equally important source of diagnostic uncertainty.

It is difficult for the clinician to make the diagnosis of ABPA with confidence, based on the medical literature. In published series, many cases satisfy *a priori* criteria only partially and may or may not be true cases of ABPA. Diagnostic imprecision is certain to diminish with the exclusion of serum eosinophil and precipitin levels as the criteria. In the present study, and in a previous large cohort of patients,² serum eosinophil and precipitin levels were neither sensitive nor specific for a diagnosis of ABPA. The continuing greater uncertainty for clinicians is whether to use essential or minimal diagnostic criteria. The question is important because a greater prevalence of ABPA due to the use of minimal criteria may influence the approach to routine investigation.

An important advantage of the routine performance of CT scanning in SPT-positive patients is that central bronchiectasis (increasingly viewed as pathognomonic of ABPA once cystic fibrosis is excluded as a diagnosis) is common to both sets of diagnostic criteria. In theory, chest radiography might be used to select patients to undergo CT scanning, with the added advantage of detecting pulmonary infiltrates. However, ABPA infiltrates are diagnosed increasingly infrequently on chest radiography as they are often asymptomatic,^{17,21} suppressed by the corticosteroid therapy that is used to treat asthma, or missed (because chest radiographs are seldom repeated in asthmatic patients in the

modern era). Furthermore, chest radiography is neither sensitive nor specific for the detection of early bronchiectasis. The false-positive rate of 14% in the present study differs little from that reported by Schwartz and Greenberger.² More importantly, three of four patients with minimal ABPA and one patient with secure ABPA would not have had their conditions diagnosed had CT been performed selectively in those with chest radiograph abnormalities.

The routine use of CT scanning in SPT-positive patients allows central bronchiectasis to be diagnosed earlier, with more precision⁸⁻¹¹ and with acceptable interobserver agreement.^{12,13} The status of patients meeting minimal but not secure criteria (increasing the possible prevalence of ABPA in patients with SPT positivity to nearly 40% in the present study) remains uncertain. Central bronchiectasis is occasionally seen in healthy subjects at autopsy and might also denote allergic fungi other than ABPA. *Curvularia* and other fungi are now known to produce a clinical picture that is similar to that of ABPA.²² Occasionally, minor bronchiectasis is seen in asthma patients without ABPA. However, studies of central bronchiectasis in asthma patients have been constrained by small numbers, a lack of diagnostic rigor (in the exclusion of ABPA), and a failure to evaluate the severity of asthma.^{9,10,13} If a diagnosis of ABPA is to be accepted on the basis of minimal criteria alone, it remains uncertain whether the isolated central bronchiectasis represents burnt-out disease or subclinical ABPA. The low serum IgE levels and weak specific IgE responses to AF would be in keeping with either hypothesis. An overreliance on IgE levels as a *sine qua non* for a diagnosis of ABPA may result in the significant underdiagnosis of ABPA in the respiratory clinic.

However, it is important that SPT-positive asthma patients with isolated central bronchiectasis are identified, in view of the destructive nature of untreated ABPA. The routine performance of CT scanning in SPT-positive patients allows the clinician to identify isolated central bronchiectasis. Even when the diagnosis of ABPA is not secured on serologic grounds, meticulous observation is still justified. Our findings indicate that this opportunity is likely to be missed if CT scanning is confined to patients with chest radiograph abnormalities.

In conclusion, SPT positivity to AF is common in the asthma clinic and is associated with a high prevalence of ABPA, justifying SPT as a screening tool in asthma patients. Central bronchiectasis is demonstrable on CT scans in approximately 40% of SPT-positive patients; thus, a diagnosis of ABPA is disclosed by CT scan in 25 to 40% of patients, depending on the choice of diagnostic criteria. The

high diagnostic yield of CT scanning supports its routine inclusion as a cost-effective component of the diagnostic algorithm.

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