
Frequency of familial occurrence in 164 patients with allergic bronchopulmonary aspergillosis

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Background: Asthma is known to run in families. Allergic bronchopulmonary aspergillosis (ABPA) occurs predominantly in patients with asthma. However, there are only 6 reports of familial occurrence over a period of 35 years.

Objective: To determine the frequency of familial occurrence in 164 patients with ABPA diagnosed over a period of 22 years in one unit.

Methods: The 164 patients with ABPA were reviewed for the occurrence of familial ABPA. Symptomatic family members were evaluated for the presence of ABPA as well as allergic *Aspergillus* sinusitis (AAS). Allergic bronchopulmonary aspergillosis and AAS were diagnosed as per criteria established.

Results: Of the 164 patients with ABPA, familial occurrence was detected in 4 pairs of first degree relatives, 2 of whom were parent–child while the other 2 were siblings. Familial ABPA was seen in 4.9% of the total patients. Of these 8 patients seven had symptoms of rhinitis while 4 had sinusitis confirmed on computed tomography of paranasal sinuses. Allergic *Aspergillus* sinusitis was detected in 3 of these 4 patients. The fourth patient with sinusitis did not consent to surgery required to confirm the diagnosis. Five of our 8 patients, prior to referral, had received antituberculous therapy. All patients responded favourably to oral prednisolone.

Conclusion: Familial occurrence was documented in 4.9% of the 164 patients with ABPA.

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INTRODUCTION

In a few individuals with asthma, repeated inhalation of the spores of the fungus *Aspergillus* evokes an immunologic response resulting in allergic bronchopulmonary aspergillosis (ABPA). This form of allergic aspergillosis was first reported more than a half-century ago in the United Kingdom by Hinson et al.¹ Despite familial preponderance of asthma, familial occurrence of ABPA is a rarity. The explanation for this remains a subject of speculation.²

One of the goals of therapy of ABPA is “to exclude ABPA in family members.”³ Despite this, familial occurrence has rarely been reported. A search of the literature revealed only 6 reports since 1973^{4–9}; of these, 1 mother and son pair was earlier described by us.⁸ This was reported because it was the first documentation of the coexistence of allergic *Aspergillus* sinusitis (AAS) and ABPA from India and was the first report of familial occurrence from this country.

Although ABPA has been documented from all continents, the frequency of occurrence of familial ABPA is yet to be determined. We have earlier reported *Aspergillus* sensitization in 28.5% of 105 patients with asthma, and ABPA was diagnosed in 8 (7.6%).¹⁰ In our series of 164 patients with ABPA, diagnosed in 1 unit over a period of more than 22 years, we document the occurrence of familial ABPA in 4 pairs of first-degree relatives. This also includes the pair

reported earlier.⁸ The paucity of such data in the literature prompted this documentation.

METHODS

Patients who had asthma with eosinophilia, those with radiologic infiltrates, and patients with a history of repeated courses of antituberculous drugs despite direct smear for AFB being constantly negative were investigated for ABPA. All patients diagnosed as having ABPA were also investigated for sinusitis. These patients were interrogated to ascertain a history of similar symptoms in their family members. After obtaining consent, symptomatic family members were investigated for ABPA. To look for a possibility of common environmental sources of exposure, the index patients and the family members were queried about their residential environment. Diagnosis of ABPA was based on 8 major criteria and 3 minor criteria^{11,12}: (1) history of asthma; (2) transient pulmonary infiltrates; (3) central bronchiectasis; (4) bands of precipitins against *Aspergillus* species; (5) type I (immediate) hypersensitivity to intradermal challenge with extracts of *Aspergillus* species (concentration 1:500 wt/vol, antigens obtained from Institute of Genomics and Integrated Biology, Delhi, a unit of the Council of Scientific and Industrial Research); (6) elevated total IgE level; and (7) elevated specific IgG or IgE against *Aspergillus fumigatus*; and (8) peripheral blood eosinophilia. The 3 minor criteria included (1) history of occasional passage of brownish plugs along with sputum; (2) sputum culture positive for *A. fumigatus*; and (3) type III (late) hypersensitivity to intradermal challenge with extracts of *Aspergillus* species.

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Table 1. Clinical and Spirometry Data in the Study Patients

Patient No., age, y (relation)	Chest symptoms					Nasal symptoms					Previous ATT	Spirometry		
	Cough	Sputum	Golden- brown plugs/ casts	Wheezing dyspnea	Watery/ mucopurulent discharge	Sneezing	Nasal blockade	Plugs/ casts	Postnasal drip	ATT		FEV ₁ , L (%)	FVC, L (%)	FEV ₁ / FVC, %
1A, 45 (mother)	+	+	+	+	—	—	—	—	—	+		2.11	3.52	60
1B, 24 (son)	+	+	+	+	+	+	+	+	+	—		2.70	4.58	59 ^a
2A, 18 (daughter)	+	+	+	+	+	+	—	—	—	—		1.41 (52)	2.10 (70)	67
2B, 37 (mother)	+	+	+	+	—	+	+	+	+	+		1.24 (49)	1.56 (53)	79 ^a
3A, 30 (brother)	+	+	—	+	+	+	—	—	—	—		3.33 (82)	4.27 (88)	78
3B, 35 (sister)	+	+	—	+	+	+	—	—	—	+		1.97 (74)	2.5 (81)	79
4A, 34 (brother)	+	+	—	+	—	+	+	—	+	+		1.59 (45)	2.65 (64)	60 ^a
4B, 30 (brother)	+	+	+	+	+	+	—	—	—	+		1.33 (37)	2.13 (50)	62

Abbreviations: ATT, antituberculous treatment; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Symbols: Plus sign, positive; minus sign, negative.

^a Patients with allergic *Aspergillus* sinusitis.

In individuals with nasal symptoms and evidence of sinusitis on plain roentgenogram, computed tomography of the paranasal sinuses was also performed. If AAS was suspected, consent was sought to obtain mycological and histopathological specimens. Patients who consented underwent an antral wash and/or Cadwell-Luc operation. Functional endoscopic sinus surgery was also performed when it became available.

The criteria adopted by us earlier^{8,13–15} and subsequently enunciated by de Shazo and Swain¹⁶ were followed for the diagnosis of AAS: (1) sinusitis of 1 or more paranasal sinuses on roentgenogram; (2) necrosed amorphous tissue along with edematous polyps infiltrated with eosinophils on histopathological evaluation of material from the sinuses; (3) demonstration of fungal elements in nasal discharge or in material obtained at the time of surgery by stain or culture; (4) absence of diabetes, previous or subsequent immunodeficiency disease, and treatment with immunosuppressive drugs; and (5) absence of invasive fungal disease at the time of diagnosis or subsequently. In addition, this was also supported by other parameters observed in ABPA.¹⁷ The institutional ethics committee approved review of the data.

RESULTS

For a period of 22 years, from 1985 to 2007, 164 patients were diagnosed as having ABPA in 1 unit. Among these 164 patients, familial ABPA was detected in 4 pairs of first-degree relatives. This was 4.9% of the total patients evaluated. Of the 4 families with familial ABPA, 2 pairs were parent-child, whereas the remaining 2 were siblings. The clinical profile and laboratory data of these 8 patients are

summarized in Tables 1–3. Seven of our 8 patients (87.5%) fulfilled all the 8 major criteria of ABPA, whereas the eighth patient (3A) satisfied 7. Regarding minor criteria, 2 patients (25%) fulfilled all 3 criteria; 3 (37.5%) fulfilled 2 criteria; and 3 others (37.5%) fulfilled 1 criterion each. All patients with AAS fulfilled all the 5 criteria. The families are numbered as per the chronological order of presentation.

In family 1, the son (patient 1B) was diagnosed as having ABPA 14 years after his mother's condition was diagnosed. In family 2, the mother (patient 2B) was diagnosed as having ABPA approximately 4 months after the diagnosis was established in her daughter (patient 2A). The brother-sister pair of family 3 presented on the same day, and their condition was diagnosed simultaneously. In family 4, both brothers' conditions were diagnosed within 1 month of each other. Although central bronchiectasis was demonstrated in all 8 patients, 3 (patients 2B, 3A, and 3B) still had preserved spirometry.

One patient from family 1 and both patients of families 2, 3, and 4 had symptoms pertaining to rhinitis. Of these 7 patients, 4, all from different families, had evidence of sinusitis on computed tomography of the paranasal sinuses. Three (patients 1B, 2B, and 4A) were subsequently diagnosed as having concomitant AAS, whereas the fourth patient (3A) did not consent to undergo the surgical procedure required to establish the diagnosis of AAS. Two of these 3 patients (1B, 2B) cultured *Aspergillus flavus* in the sinus wash, whereas the third (4A) cultured *A. fumigatus*.

On the basis of their clinical and radiologic profiles, 5 of these 8 patients, before referral, were prescribed antitubercu-

Table 2. Immunological and Pathological Data in the Study Patients

Patient No., age, y (relation)	Peripheral blood eosinophils, %	Intradermal testing with <i>Aspergillus</i> antigens	Total IgE, IU/mL	Specific IgG/IgE against <i>Aspergillus</i>	Precipitins against <i>Aspergillus</i>	Fungal culture of sputum	Fungal culture of nasal discharge	Sinus wash/biopsy	
								Allergic mucin	Biopsy and presence of fungal elements
1A, 45 (mother)	18	<i>A fumigatus</i> <i>A flavus</i>	12,500	+/+	<i>A fumigatus</i>	<i>A fumigatus</i>	—	—	—
1B, 24 (son)	9	<i>A fumigatus</i> <i>A flavus</i>	5,600	+/+	<i>A fumigatus</i> <i>A flavus</i>	<i>A fumigatus</i> <i>A flavus</i>	<i>A flavus</i>	+	<i>A flavus</i> ^a (culture)
2A, 18 (daughter)	13	<i>A fumigatus</i>	7,294	+/+	<i>A fumigatus</i>	—	—	—	—
2B, 37 (mother)	22	<i>A fumigatus</i> <i>A flavus</i> <i>A niger</i>	1,822	+/+	<i>A fumigatus</i>	—	<i>A flavus</i>	+	<i>A flavus</i> ^a (culture)
3A, 30 (brother)	1	<i>A fumigatus</i> <i>A flavus</i> <i>A niger</i> <i>A tamari</i>	2,276	+/+	<i>A fumigatus</i>	—	—	—	—
3B, 35 (sister)	16	<i>A fumigatus</i> <i>A flavus</i> <i>A niger</i> <i>A tamari</i>	4,048	+/+	<i>A flavus</i>	—	—	—	—
4A, 34 (brother)	20	<i>A fumigatus</i> <i>A flavus</i> <i>A niger</i> <i>A tamari</i>	2,839	+/+	<i>A fumigatus</i>	—	—	+	<i>A fumigatus</i> ^a (culture)
4B, 30 (brother)	13	<i>A fumigatus</i> <i>A flavus</i> <i>A niger</i> <i>A tamari</i>	17,015	+/+	<i>A fumigatus</i>	—	—	—	—

Symbols: Plus sign, positive; minus sign, negative.

^a Patients with allergic *Aspergillus* sinusitis.

Table 3. Radiological Data in the Study Patients

Patient No., age, y (relation)	Chest X-ray results	Chest CT/bronchography results	PNS X-ray examination findings	Sinusitis on CT PNS
1A, 45 (mother)	Transient pulmonary infiltrates	Central bronchiectasis		
1B, 24 (son)	Transient pulmonary infiltrates	Central bronchiectasis	Right maxillary sinus haziness	Maxillary and ethmoidal ^a
2A, 18 (daughter)	Transient pulmonary infiltrates	Central bronchiectasis		Inferior turbinate hypertrophy
2B, 37 (mother)	Transient pulmonary infiltrates	Central bronchiectasis with mucoid impaction and pretracheal and precarinal lymph nodes	Right maxillary sinusitis	Maxillary and frontal ^a
3A, 30 (brother)	Transient pulmonary infiltrates	Central bronchiectasis	B/L maxillary sinusitis with B/L polyp	Maxillary sinusitis with B/L maxillary polyp
3B, 35 (sister)	Transient pulmonary infiltrates	Central bronchiectasis		Turbinate hypertrophy
4A, 34 (brother)	Transient pulmonary infiltrates	Central bronchiectasis with mediastinal nodes	Right maxillary sinusitis	Maxillary and frontal ^a
4B, 30 (brother)	Transient pulmonary infiltrates	Central bronchiectasis		Inferior turbinate hypertrophy

Abbreviations: B/L, bilateral; CT, computed tomography; PNS, paranasal sinuses.

^a Patients with allergic *Aspergillus* sinusitis.

Table 4. Clinical and Spirometry Data From Previously Published Reports

Patient No. (reference No.), age, y (relation)	Chest symptoms			Nasal symptoms					Previous ATT		Spirometry		
	Cough	Sputum	Golden- brown plugs/ casts	Wheezing dyspnea	Watery/ mucopurulent discharge	Sneezing	Nasal blockade	Plugs/ casts	Postnasal drip	ATT	FEV ₁	FVC	FEV ₁ / FVC
1A (4), 12 (son)	+	+	—	+	—	—	—	—	—	—	No data	No data	No data
1B (4), 13 (son)	+	+	—	+	—	—	—	—	—	—	No data	No data	No data
1C (4), 40 (mother)	+	+	—	+	—	—	—	—	—	+	Mild obstruction with increased RV	No data	No data
2A (5), 24 (brother)	+	+	+	+	+	—	—	—	—	—	Normal	Normal	Normal
2B (5), 22 (brother)	+	+	+	+	+	—	—	—	—	—	Normal	Normal	Normal
3A (6), 18 (sister)	+	+	—	+	No data	No data	No data	No data	No data	Atypical	Normal	Normal	Normal
3B (6), 16 (brother)	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
4A (7), 48 (father)	+	+	—	+	+	+	—	—	—	—	No data	No data	No data
4B (7), 20 (daughter)	+	+	—	+	+	+	—	—	—	—	No data	No data	No data
6A (9), 37 (sister)	+	+	—	+	+	+	+	—	+	+	Reversible	airway obstruction	
6B (9), 20 (brother)	+	+	—	+	+	+	—	—	—	—	No data	No data	No data

Abbreviations: ATT, antituberculous treatment; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume.
 Symbols: Plus sign, positive; minus sign, negative.

Table 5. Immunological, Pathological, and Radiological Data From Previously Published Reports

Patient No. (reference No.), age, y (relation)	Peripheral blood eosinophils	Intradermal testing with <i>Aspergillus</i> antigens	Total IgE, IU/mL	Specific IgG/ IgE against <i>Aspergillus</i>	Precipitins against <i>Aspergillus</i>	Fungal culture of sputum	Fungal culture of nasal discharge	Sinus wash/biopsy		Radiology	
								Allergic <i>mucin</i>	Biopsy and fungal elements	Chest X-ray/ PNS X-ray examination results	Chest CT/ bronchography results
1A (4), 12 (son)	4%	<i>A fumigatus</i>	No data	No data	<i>A fumigatus</i>	No data	No data	No data	No data	TPI	No data
1B (4), 13 (son)	5%	<i>A fumigatus</i>	No data	No data	<i>A fumigatus</i>	No data	No data	No data	No data	TPI	No data
1C (4), 40 (mother)	6%	<i>A fumigatus</i>	No data	No data	<i>A fumigatus</i>	<i>A fumigatus</i>	No data	No data	No data	Right upper lobe infiltrates	No data
2A (5), 24 (brother)	13%	<i>A fumigatus</i>	3,700	+/+	<i>Aspergillus</i> sp	<i>A fumigatus</i>	No data	No data	No data	Prominent BV markings in left lung	No CB on bronchography
2B (5), 22 (brother)	11%	<i>A fumigatus</i>	1,960	+/+	<i>Aspergillus</i> sp	<i>A fumigatus</i>	No data	No data	No data	Mild hyperinflation with perihilar shadow	CB in bronchography
3A (6), 18 (sister)	3%	<i>A fumigatus</i>	794	No data	<i>A fumigatus</i>	<i>A fumigatus</i>	No data	No data	No data	TPI	CB in bronchography
3B (6), 16 (brother)	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
4A (7), 48 (father)	No data	<i>Aspergillus</i> mix	3,482	+/+ <i>A fumigatus</i> , <i>A niger</i>	<i>A fumigatus</i> , <i>A niger</i>	No data	No data	No data	No data	Peribronchial cuffing with bronchiectasis	Normal
4B (7), 20 (daughter)	No data	<i>Aspergillus</i> mix	3,888	+/+ IgG against <i>A</i> <i>fumigatus</i> , <i>A niger</i>	<i>A fumigatus</i> , <i>A niger</i>	No data	No data	No data	No data	Normal	CB
6A (9), 37 (sister)	15%	<i>A fumigatus</i>	5,002	IgG +	No data	No data	No data	No data	No data	TPI, B/L maxillary haziness	CB
6B (9), 20 (brother)	No data	No data	No data	No data	No data	No data	No data	No data	No data	TPI	No data

Abbreviations: ATT, antituberculous treatment; B/L, bilateral; BV, bronchovascular; CB, central bronchiectasis; CT, computed tomography; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PNS, paranasal sinuses; RV, residual volume; TPI, transient pulmonary infiltrates.

Symbol: Plus sign, positive.

lous therapy. Once the diagnosis of ABPA was established, all patients were given oral prednisolone, with which there was remarkable symptomatic and radiologic improvement. All patients also received concomitant treatment for asthma and/or rhinitis, along with other supportive therapy. Patients of families 1, 2, and 4 are still participating in regular follow-up, but patients of family 3 were lost to follow-up. All the 6 patients are well controlled with therapy. Patient 1A (mother) has long-standing *Pseudomonas* colonization, which causes exacerbations requiring hospitalization once or twice a year.

DISCUSSION

We report the familial occurrence of ABPA in 8 of the 164 patients (4.9%) who were available to us for evaluation. Although familial ABPA was first documented in 1973,⁴ there are, to date, only 5 other reports⁵⁻⁹ available in the literature. Five of these reports are detailed in Table 4 and Table 5; the sixth one, published by us in 1990,⁸ is included with the current series. The patients described in the aforementioned reports were all first-degree relatives, as seen in the group that is being presented.

The postulate that asthma runs in families has been demonstrated by higher concordance and correlation of asthma in monozygotic twins compared with dizygotic ones.¹⁸ Furthermore, the risk of asthma is 1.6 times greater in patients with both parents having asthma.¹⁹ Similarly, genetic and environmental factors probably play an important role in the familial occurrence of ABPA. In view of this, the rarity of ABPA in first-degree relatives is rather surprising. In 1979, Graves et al⁵ evaluated a mother and 2 sons with asthma. Both the sons were subsequently diagnosed as having ABPA, although all 3 were patients with asthma who were exposed to the same environment. It was observed that both the sons shared identical HLA serotypes (A 28, 26; B 35, 18; CW4), whereas the mother's HLA (A 31, 26; B 40, 18; CW3) was different. The authors postulated that the occurrence of ABPA, in both sons only, could be due to variations in the "inherited immune responsiveness," despite similar environmental exposure to *Aspergillus*. Chauhan et al²⁰ have suggested that patients with HLA-DR2 alleles DRB1*1503 and DRB1*1501 are susceptible to ABPA. The study also revealed that HLA-DQ2 could possibly confer protection against ABPA. This disease is well known to occur in patients with cystic fibrosis. In a study of 11 patients with ABPA without cystic fibrosis, the authors found that 6 of these 11 patients carried cystic fibrosis transmembrane regulator (*CFTR*) gene mutations.²¹ One patient carried 2 CF mutations ($\Delta F508/R347H$), whereas 5 had 1 CF mutation ($\Delta F508$ in 4 patients and R117H in 1 patient). The authors postulated that the *CFTR* gene could play a possible etiological role in ABPA.

Halwig et al⁷ reported a father-daughter pair with familial ABPA and investigated the possibility of a common environmental source. On evaluation of the family's home, the investigators grew *Aspergillus niger* and *A fumigatus* from the central humidifier. The culture of *A niger* grown from the humidifier resulted in precipitin reaction in the serum

from the father as well as the daughter. The father also demonstrated elevated specific IgG and IgE against *A fumigatus* and specific IgG against *A niger*, whereas the daughter demonstrated specific IgG antibodies against *A niger* as well as *A fumigatus*. The authors postulated that a probable common environmental source of *Aspergillus* spores could permit colonization of bronchial tree and result in ABPA.

Of the 5 families described earlier,^{4-7,9} symptoms of rhinitis were documented in 3 families.^{5,7,9} Although there was no mention of nasal symptoms in the report by Greenberger and Katzenstein,⁶ the authors recorded that the sister of the sister-brother pair underwent nasal anastomosis for persistent sinusitis. In the recently described sister-brother pair,⁹ both patients had symptoms of rhinitis but were not investigated further. However, the diagnosis of ABPA in the brother was not convincing because the diagnosis was solely based on "bilateral migratory shadows." None of the previously described 5 families were evaluated for involvement of the paranasal sinuses. Our report highlights the need to evaluate nasal symptoms in patients because 4 of our 7 patients (57%) with rhinitis had sinusitis. Of these 4 patients, 3 were subsequently diagnosed as having AAS. As seen in an earlier report,^{22,23} 2 of these 3 patients also cultured *A flavus* from the sinus wash. The fourth patient with sinusitis (3A) did not consent to the surgical procedure required to establish the diagnosis of AAS.

The acronym SAM (sinobronchial allergic mycosis) syndrome was coined to describe the occurrence of concomitant AAS and ABPA in the same patient.²⁴ The authors postulated that this was an expression of fungal hypersensitivity in both the upper and lower airways. We had previously reported that the co-occurrence of ABPA and AAS may not be as rare as it appears.²⁵ Because oral corticosteroids remain the cornerstone of treatment of both diseases, it appears that common immunopathological processes are involved. This further strengthens the current concept of a "unified airways disease." Thus, it is important to look for AAS in patients with ABPA and ABPA in patients with AAS.

The clinical and radiologic picture of ABPA often simulates pulmonary tuberculosis and causes a diagnostic dilemma in areas with high tuberculosis prevalence. These patients often receive antituberculous therapy while lung damage continues to occur. Five of our 8 patients had received antituberculous therapy before presentation.

In summary, familial occurrence of ABPA was seen in 4.9% of our patients. The genetic and environmental factors, which dictate the immune responsiveness in atopic individuals, could possibly play an important role in the familial presence of the disease in first-degree relatives. Although the preponderance of ABPA in families does not appear to be common, it is important to look for the disease in other family members, especially in those with a personal history of atopy.

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