Original research

Prevalence of various allergen sensitizations in severe atopic asthma in eastern India

Jayanti Ray[1], Angira Dasgupta[2], Subhadip Mukherjee[3], Parthasarathi Bhattacharyya[4]

[1]RMO-cum-clinical tutor, Department of Medicine, Kolkata Medical College,[2]Department of Medicine, B R Singh Hospital and centre for medical education and research, Kolkata, [3]Peerless Hospital and B K Roy Research Centre, Kolkata, [4] Director, Institute of Pulmocare and Research, Kolkata

Abstract

Introduction: Atopic asthma is caused by sensitization to various allergens including a variety of fungi. Fungal sensitized asthma can be due to Allergic Broncho Pulmonary Aspergillosis (ABPA) or due to the recently recognised phenotype severe asthma with fungal sensitization (SAFS). However, little is known about the prevalences of each of these in India and perhaps none from eastern India.

Aim: The aim of this study was to find out the prevalence of atopic asthma, SAFS, ABPA and other common non fungal allergen sensitisers in severe asthma.

Methods: This is a cross-sectional study over 6 months in two severe asthma referral clinics of Kolkata. Consecutive severe asthma patients were identified as atopic based on serum IgE levels (>120kU/l). Atopic patients underwent blood tests (specific IgE) for 10 commercially available common allergens (Phadia, Immunocap 250).

Results: Of 91 patients 70 (76.9%) were atopic. Of these 70 atopic subjects, 35(50%) were sensitized to Aspergillous, 18 (25.7%) had ABPA according to Rosenberg criteria and 27 (38.5%) had SAFS. 11 of the 27 SAFS patients were not sensitized to Aspergillous. Amongst non fungal sensitisers, cockroach was the most prevalent followed by dermatophgoides.

Conclusion: There is a high prevalence of SAFS and ABPA among severe atopic asthmatics attending severe asthma clinics in eastern India. Patients should be tested routinely for these subsets of severe asthmatics as treatment strategies are different.

Key Words: severe atopic asthma, fungal sensitization, prevalence
(The Pulmo-Face; 2015, 15:1, 14-18)

Abbreviations

ABPA- Allergic Broncho Pulmonary Aspergillosis
SAFS- severe asthma with fungal sensitization
ICS- inhaled corticosteroids
SPT- skin prick test

INTRODUCTION

Atopic asthma is defined by the presence of allergen-specific IgE (1). Several allergens such as house dust mites, cockroach or animal dander and fungus have long been implicated in severe atopic asthma. Severe asthma with fungal sensitization (SAFS) is a recently recognized novel phenotype of severe atopic asthma (2). Fungal exposure has also been linked to loss of asthma control requiring multiple hospital and intensive care admissions (3, 4), In addition, it may be a cause of asthma onset in both children and adults and has recently been shown to be associated with increased severity of disease (5, 6).

A wide variety of fungi have been implicated,the most common agents being Ascomycota, including Alternaria, Aspergillus, Penicillium, and Cladosporiumspp (7). Aspergillus fumigatus in particular has been associated with more severe asthma (2), with pooled prevalence of sensitization

Corresponding Author

Dr. Angira Dasgupta
Department of Medicine,
B R Singh Hospital and Centre for Medical Education and Research, Kolkata.

Email :angiradasgupta@gmail.com

in 28% of asthmatics seen in specialty clinics (8). Sensitization to A. fumigatus is associated with lower lung function in asthma (9), and antifungal therapy improves symptoms in severe asthmatics with fungal sensitization (SAFS) (10).

Little is known about the prevalence of SAFS or ABPA and common sensitizers of severe atopic asthma in India. This is because the use of tests such as allergen specific IgE tests for estimation of sensitizers is still not routine practice in many parts of the country. The main reason is probably non availability of standardized tests across all centers.

The main objectives of this study are to find out the 1) prevalence of atopic asthma, SAFS and ABPA amongst severe asthmatics, and 2) common non fungal allergen sensitizers in severe atopic asthma.

METHODS

Study design:

This was a cross-sectional study over 6 months involving two severe asthma referral clinics in the heart of Kolkata. Ethics clearance was obtained from the respective Institutional Review Boards. Written informed consent was taken from all participants.

Study Population

All severe asthma patients with current or history of documented reversibility in airflow limitation (detailed below) with age >12 years who attended two referral asthma clinics during the study period were included. Exclusion criteria includeda) the patients with co-morbidities that might affect asthma control (associated uncontrolled cardiac diseases, neuropsychiatry disorders), b) pregnant patients, c) patients with overt organ dysfunction such as heart failure, renal failure, and d) those who did not sign the consent.

Study definitions

Asthma was defined by current or historical evidence of reversible (increase in FEV1 by 12% and 200ml after inhalation of 400mcg of salbutamol with the use of metered dose inhaler)airflow obstruction as per to the American Thoracic Society (ATS) recommendations (11). Asthma was considered atopic when the serum IgE ≥120 kU/l (12).

Severe asthma was defined as "asthma which requires treatment with high dose inhaled corticosteroids (ICS) (>800 mcg of budesonide or equivalent) plus a second controller (and/ or systemic CS) to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy" (13).

SAFS was defined by previous published critreria (1) that included (a) severe asthma, (b) total IgE< 1000 kU/L, and (c) positive skin test or raised specific IgE to any fungus (2).

The diagnostic criteria for ABPA included (i) asthma (of any severity), (ii) total serum IgE>1000 kU/L, (iii) immediate cutaneous reaction to A. fumigatus of >3 mm compared with control or (iv) elevated A. fumigatus-specific serum IgE levels, (v) precipitating antibodies toA. fumigatus in the serum, (vi) a history of pulmonary infiltrates (transient or fixed), (vii) central bronchiectasis (CB), (viii) a history of expectoration of brown plugs or flecks, and (ix) isolation of A. fumigatus from the sputum (12,13), of which (ii) and (iv) were essential (16).

Study method (figure 1)

Consecutive asthma patients (diagnosed by spirometry) were examined in detail and their medical history and symptom questionnaires were obtained. All patients had spirometry with bronchodilator reversibility done. Severe asthma patients had serum total IgE tests (Siemens) and/

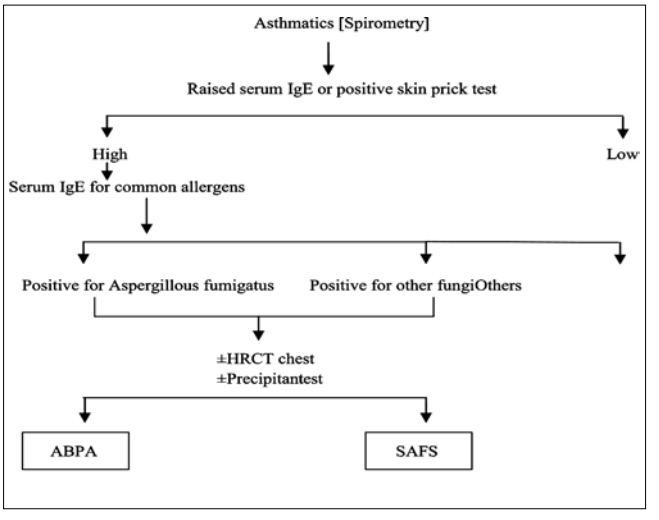

Figure 1: Study methodology

or skin prick test. Patients with raised IgE levels underwent blood tests (specific IgE) for common allergens (Phadia, Immunocap 250). Patients with elevated specific IgE for A. fumigatus were thereafter evaluated for the presence of ABPA by above criteria for ABPA.

Statistical Analysis

Data was collected and recorded in Microsoft excel. Statistical analysis was done in SPSS (version 19). Continuous data was expressed as mean and standard deviation when normally distributed. Skewed data was expressed as median and range. Proportions were expressed as percentages.

RESULTS

A total of 91 severe asthmatics were included in this study. 70 (76.9%) of them were atopic. Of these 70 atopic subjects, 35(50%) were sensitized to Aspergillous; however, 18 (25.7%) had ABPA according to Rosenberg criteria and 27 (38.5%) had SAFS (figure 2).11 of the 27 SAFS patients were not sensitized to Aspergillous.

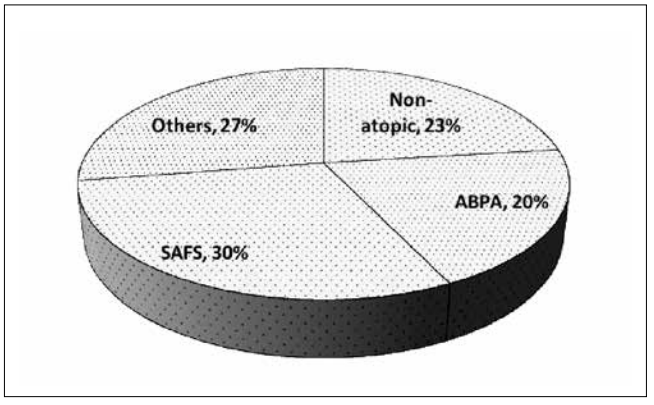

Figure 2 : Prevalence (in percentages; n=91) of the\various phenotypes (according to allergen sensitization) of severe asthma

The demographic characteristics of these patients are shown in Table 1.

Parameter	All subjects, n=91	Non-Atopic, n=21	ABPA, n=18	SAFS, n=27	Others, n=25
Age in years; mean(SD)	53.9 (14.3)	57.8 (11.30)	51.8 (16.6)	56.5 (14.8)	49.6 (13.1)
M:F	57 : 34	14 : 7	14:4	18 ; 9	11:14
Smoker (%)	35 (38.5%)	8 (38%)	9 (50%)	11 (40.7%)	7 (28%)
FEV1 in Litres; mean (SD)	1.40 (0.65)	1.39 (0.73)	1.39 (0.73)	1.45 (0.68)	1.38 (0.51)
S. IgE in kU/l ; Median (min, max)	467.4 (14.8, 6342.1)	40.7 (5.9, 82.3)	1910.1 (1067.5, 6342.1)	481.8 (122.6, 1755.2)	439.6 (122.9, 1134)

Table 1: Demographic data of the various groups

The prevalence of sensitization to the various allergens tested is shown in Figure 3.

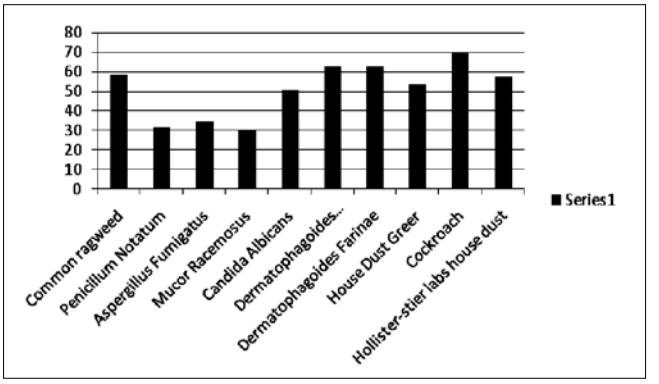

Figure 3: Prevalence of the various allergen sensitizations

DISCUSSION

This study is perhaps the first study from eastern India, which has characterized the allergy profile of severe asthma patients. This study reveals the huge burden (30% of severe asthma patients) of fungal sensitization in severe asthma (SAFS) which usually goes unrecognized and often not given special attention. Allergy to Cockroach and Dermatophagoides were the most common allergens. Many patients with fungal sensitisation also had concomitant allergy to Dermatophagoides.

Our study was able to identify three major phenotypes of severe atopic asthma (ABPA, SAFS and other non-fungal allergy) based on allergy sensitization as measured by specific IgE to 10 common and commercially available allergens (Common Ragweed, Penicillium Notatum,Aspergillous Fumigatus, Mucor Racemosus, Candida Albicans, Dermatophagoides Pternyssinus, Dermatophagoides Farinae, House Dust Greer, Cockroach and Hollister-stier labs house dust) in India. The prevalence of ABPA was high as is expected to occur in severe asthmatics attending referral clinics (17). However, the largest phenotype was that of SAFS. The importance of identifying this entity is in being able to offer treatment with antifungals such as azoles (itraconazole, voriconazole, posaconazole) as suggested in recent clinical trials (10,18). The exact treatment duration with antifungals in SAFS is yet to be worked out. However, few studies have shown

an improvement in quality of life, improvement in rhinitis score, and decrease in IgE level with use of antifungal treatment in SAFS (10, 18).

The precise prevalence of fungal sensitivity is unclear in India and even in countries such as the US. The National Health and Nutrition Examination Survey III study (19) reported that among US citizens aged 6 to 59 years, 12.9% have positive skin prick test (SPT) responses to Alternaria species, whereas in another US study 21% of 102 atopic subjects had positive skin test results to 1 or more fungal allergens.(20). In European studies 78% of 824 Spanish patients with allergic respiratory symptoms had positive SPT responses to Alternaria species (21). Although various studies report that 12% to 42% of atopic patients are mold sensitive (21-22) others are as high as 80% (23).

The main drawback of this study is the small sample size. This is due to the fact that patients were mainly recruited from two severe asthma referral clinics situated in the same city. However, these two clinics get severe asthma referrals from a major part of West Bengal. Another drawback is that we could not test for other common allergens such as Alternaria and Cladosporium due to non availability of these tests commercially. Future larger multicenter epidemiologic studies using newer diagnostic approaches, such as fungal enzyme microarrays, fluorescent halogen immunoassays, and other approaches, might allow for a more accurate assessment of fungal sensitization and other allergies in severe asthma.

REFERENCES:

1. Szefler SJ, Wenzel S, Brown R, Erzurum SC, Fahy JV, Hamilton RG, Hunt JF, Kita H, Liu AH, Panettieri RA Jr, Schleimer RP, Minnicozzi M.Asthma outcomes: biomarkers. J Allergy ClinImmunol. 2012 Mar;129(3 Suppl):S9-23. doi: 10.1016/j.jaci.2011.12.979
2. Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. EurRespir J 2006; 27(3):615–626.
3. Agarwal R, Nath A, Aggarwal AN, Gupta D, Chakrabarti A. Aspergillus hypersensitivity and allergic bronchopulmonaryaspergillosis in patients with acute severe asthma in a respiratory intensive care unit in North India. Mycoses 2009; 53(2):138–143.
4. O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. BMC Pulm Med 2005; 5:4.
5. Knutsen, AP, Bush RK,Demain JG, et al.Fungi and allergic lower respiratory tract disease. J. Allergy Clin. Immunol. 2012; 129: 280–291.
6. Zureik M, Nuekirch C, Leynaert B, et al. Sensitization to airborne moulds and severity of asthma: cross sectional study from European community respiratory healthsurvey. Br. Med. J. 2002 325: 411–414.
7. Agarwal R, Gupta D. Severe asthma and fungi:current evidence. Med. Mycol. 2011, 49(Suppl. 1): S150–S157.
8. Agarwal R, Agarwal A N, Gupta D, Jindal S K. Aspergillus hypersensitivity and allergic bronchopulmonaryaspergillosis in patients with bronchial asthma: systematicreview and meta-analysis. Int. J. Tuberc. Lung Dis. 2009; 13: 936–944.
9. Fairs A, Agbetile J, Hargadon B, et al. IgE sensitization to Aspergillus fumigatus is associated with reduced lung function in asthma. Am. J. Respir. Crit. Care Med. 2010; 182:1362–1368.
10. Denning D W, O'Driscoll B R, Powell G, et al.. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization. The fungal asthma sensitization (FAST) study. Am. J. Respir. Crit. Care Med.2009; 179: 11–18.
11. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med. 1995;152:1107–36.
12. Borish L, Chipps B, Deniz Y, Gujrathi S, Zheng B, Dolan CM. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol. 2005; 95:247–53.
13. Chung K F, Wenzel S E, Brozek J L, Bush A, Castro M, Sterk P J, et al. International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma. Eur Respir J. 2014 Feb; 43(2):343-73.
14. Ricketti AJ, Greenberger PA, Mintzer RA, Patterson R. Allergic broncho pulmonary aspergillosis. Arch Intern Med 1983; 143(8):1553–1557.
15. Patterson R, Greenberger PA, Harris KE. Allergic bronchopulmonary aspergillosis. Chest 2000; 118(1) : 7–8.

16. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis.Ann Intern Med. 1977 Apr;86(4):405-14.

17. Sarkar A, Mukherjee A,Ghoshal AG, Kundu S, Mitra S. Occurrence of allergic bronchopulmonary mycosis in patients with asthma: An Eastern India experience. Lung India. 2010 Oct-Dec; 27(4):212–216.

18. Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. J Asthma. 2012 May;49(4):423-33.

19. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol 2005; 116:377-83.

20. Beezhold DH, Green BJ, Blachere FM, Schmechel D, Weissman DN, Velickoff D, et al. Prevalence of allergic sensitization to indoor fungi in West Virginia. Allergy Asthma Proc 2008;29:29-39.

21. Bartra J, Belmonte J, Torres-Rodriguez JM, Cistero-Bahima A. Sensitization to Alternaria in patients with respiratory allergy. Front Biosci 2009;14:3372-9.

22. Gonianakis MI, Neonakis IK, Gonianakis IM, Baritaki MA, Bouros D, Potamias G, et al. Mold allergy in the Mediterranean Island of Crete, Greece: a 10-year volumetric,aerobiological study with dermal sensitization correlations. Allergy Asthma Proc 2006;27:354-62.

23. Horner WE, Armstrong M, El-Dahr J, McCants M, Reese G, Kobernick AK, et al. Prevalence of IgE reactivities in mold-allergic subjects to commercially available fungal enzymes. Allergy Asthma Proc 2008;29:629-35.