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Role of Fungi (molds) in allergic airway disease -An Analysis in a South Indian Otolaryngology center

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Abstract

Fungal spores are abundant in nature and much evidence is now available to show that fungi can cause atopic clinical illnesses. Many of these fungal spores are lesser than 10 microns in diameter and their deposition into lower airways is common. Fungal sensitization is a significant risk factor for developing asthma in later part of life. Molds grow indoors and outdoors. The two most commonly occurring outdoor molds are *Alternaria* and *Cladosporium*. The most common indoor moulds are *Penicillium, Aspergillus* and *Mucor* that are causing symptoms throughout the year to patients.

A study was done on the data related to 550 patients visiting the ENT clinic with symptoms related to respiratory allergies during the period from January 2000 to September 2009. The patients were divided into 3 groups based on clinical findings allergic rhinitis, allergic rhinitis with asthma and allergic fungal sinusitis. Investigations were done that included total serum IgE levels, peripheral eoisinophil (percentage) and skin tests. Treatment was given with antihistamines (oral and topical), steroid nasal sprays, inhalers and subcutaneous immunotherapy. The results of investigations and skin tests are discussed in this paper.

Key words: Allergy patients, fungal sensitization, total serum IgE, peripheral eosinophil (%), skin tests, otolaryngology center.

Abbreviations: Allergic Rhinitis (AR), Allergic Rhinitis with asthma (AR with asthma), Allergic Fungal Sinusitis (AFS), Enzyme Linked Fluorescent Assay (ELFA), immunoglobulin E (IgE), house dust mite (HDM), skin prick test (SPT).

INTRODUCTION

People are exposed to aeroallergens in various settings, both at home and at work. Fungi are ubiquitous airborne allergens and are important causes of human diseases, especially in the upper and lower respiratory tracts. Allergy is one form of human disease which affects about 20% of the population. A number of allergens associated with various forms of allergy have been reported from all over the world[1, 2].

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The concentration of allergens in the environment varies, depending on various factors including climate, vegetation, and air quality. The outdoor allergens are predominantly constituted by plant pollens and fungal spores. The indoor allergens, on the other hand, are represented by allergens from dust mites, cockroaches and pets. Fungal spores also have been reported from the indoor environment[3]. The concentration and prevalence of the indoor allergens vary substantially and are dependent on moisture content, ventilation, and the presence or absence of pets, carpets, and houseplants[4].

Fungi from human environment or growing in human body may cause allergic reactions. They are

associated with number of allergic diseases in humans including allergic rhinitis, conjunctivitis, bronchial asthma and allergic broncho pulmonary mycoses resulting from exposure to spores[5]. The prevalence of respiratory allergies to fungi is estimated at 20% to 30% among atopic individuals and up to 6% in general population[2, 6, 7]. The most common fungal allergens are *Alternaria, Cladosporium, Asperigillus, Penicillium* and yeasts[8].

Clinically the presenting symptoms associated with allergy are sneezing, nasal discharge, coughing, wheezing, and shortness of breath. Reversible pulmonary airway obstruction, angiodema, urticaria, and even anaphylaxis may manifest in these patients. Although an allergic reaction to fungal allergens is suggested as an important contributing factor in development of respiratory symptoms, other mechanisms, such as increased exposure to fungal metabolites, mycotoxins and other compounds of immunosuppressant or irritant properties may also be important [9].

Several epidemiological and diagnostic studies have reported an increasing prevalence of allergic reactivity to fungi assessed with use of skin testing or specific IgE detection [9]. However, the exact prevalence of fungal sensitization is not known, mainly due to lack of standardized fungal extracts and due to overwhelming number of fungal species that are able to elicit IgE mediated reactions[5]. The effective in vivo and and in vitro diagnosis of fungal allergies is based on availability of well-characterized allergen preparation[10].

The present study is aimed at determining the prevalence of IgE mediated allergy to fungi, as well as contribution of sensitization to fungi with respect to allergic manifestations to establish a relationship between the anemophilous fungi isolated in the air and patients with respiratory allergy, and to show the fungal extracts that could provoke skin test reactivity in individuals with respiratory allergy (allergic rhinitis, asthma) in a south Indian clinic.

MATERIALS AND METHODS

A retro prospective study was conducted on 570 patients who visited allergy clinic from January 2000 to September 2009.

All patients were subjected to full ENT examination. Patients were selected based on symptoms of sneezing, watery rhinorrhoea, nasal obstruction, eye symptoms (in the form of redness, watering of eyes and itching), itching of nose, throat and ear and any asthma related symptoms. Investigations done on such patients included total serum IgE (by ELFA method), peripheral eosinophil (%), skin tests (done using commercially available antigens); X-ray/CT scan of paranasal sinuses, nasal endoscopy and spirometry were done wherever it was needed.

Based on clinical findings and investigations done, patients were categorized into three groups 1) Allergic Rhinitis (AR) 2) Allergic Rhinitis (AR) with asthma 3) Allergic Fungal Sinusitis (AFS). Skin tests were performed on 290 individuals. Based on positivity to skin tests individuals were categorized into 3 groups based on their difference in sensitivity to antigens in different category of respiratory allergies.

1) Positive towards Fungus

2) Positive towards allergens other than fungus (HDM, Pollen, Insects, Food etc...)

3) Positive towards other allergens and fungus.

Among individuals who were skin test positive towards fungal allergens, individuals sensitized to specific type of fungi were identified through skin tests in different categories of respiratory allergy patients.

Patients were excluded from the study if they had clinical features of vasomotor rhinitis, COPD, if they had received treatment of corticosteroid or the other immunosuppressive therapy during preceding 6 months, if they had elevated IgE level caused by another disease or if they had ever received allergen immunotherapy.

Anterior rhinoscopy was done with sterilized nasal speculum to verify the presence or absence of polyps or hypertrophy of turbinates or any other local pathology. Standard examination of throat and ear was also done. Fungal culture was done on patients' nasal exudation to determine the type of fungi for which the individual was sensitized.

Total IgE levels, peripheral eosinophil (%) were

estimated in 3 groups of patients who were with differing in their sensitivity towards allergens and their means were compared in different categories of respiratory allergy patients.

DATA ANALYSIS

Age group of individuals who visited the allergy clinic and also for the individuals who were sensitized to different allergens among various categories of respiratory allergy patients was calculated through one sample t-test. Mean levels of IgE, peripheral eosinophil (%) were determined and compared in individuals differing in their allergen sensitivity, among various groups of respiratory allergic patients through one sample t-test. The analysis was performed by using SPSS-17.0. Total serum IgE levels, peripheral eosinophils (%) was obtained at 95% confidence interval with p value <0.05 considered to be significant.

RESULTS

Data obtained on patients' demographic characters (Age, Gender) who had visited the allergy clinic is given in table 1.Individuals on whom skin test was conducted is given in fig1, Gender and age of individuals on whom skin test was conducted is given in table 2. Among skin tests performed, 68.4% were intra dermal and 31.6% were skin prick tests, 84.13% of individuals were found positive and 18.18% were found negative towards allergen sensitivity. From the positive skin tests obtained, number of patients sensitized to specific type of allergens were categorized; their demographic characters (Age and Gender) are given in table 3 (fig 2). Based on allergen sensitivity, number of individuals who were sensitized to specific allergen among various groups of Respiratory allergy patients is given in table 4 (i and ii) (fig 3). Type of specific fungi was identified in all subjects who were found fungal positive is given in table 5. Individuals on whom fungal culture was conducted, positivity towards fungal culture and type of fungi isolated in culture is given in fig 4. Comparative Mean total IgE and peripheral eosinophil (%) among various groups of respiratory allergic individuals differing in their allergen sensitivity is given in table 6 and table 7 (fig 5, fig 6, fig7,fig 8, fig 9 and fig 10).

Table 1. Descriptive characteristics of patients who visited the allergy clinic

	Males (%)	Females (%)	Total
Number of Individuals	292 (51.2%)	278 (48.8%)	570 (100%)
Age of Individuals(Mean ± S.D)	38.23±11.03 yrs*	36.10 ± 11.45 yrs*	37.03±11.25 yrs*

*p<0.01 was considered to be significant

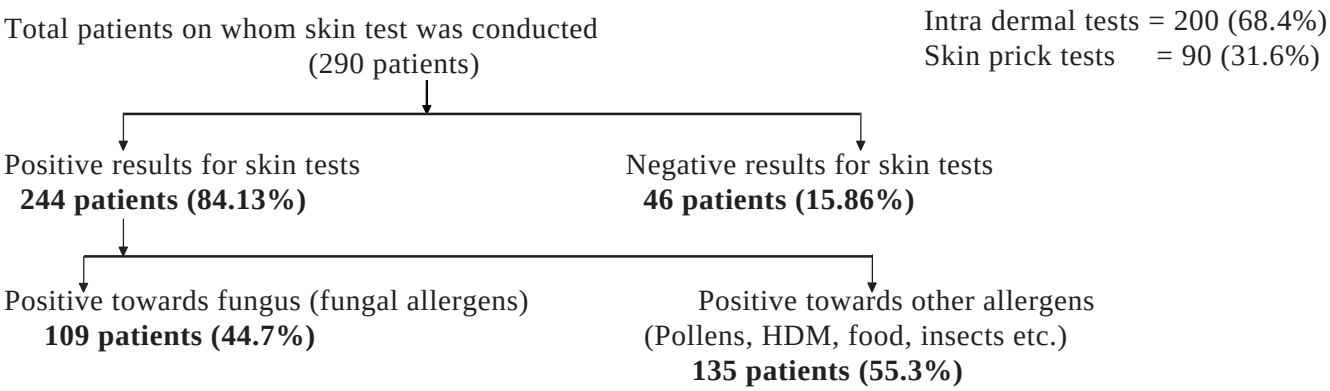

Fig 1: **Flow chart showing number of individuals on whom skin tests were conducted**

Table 2. Gender and age of individuals on whom skin tests were conducted

	Males (%)	Females (%)	Total
Number of individuals	148 (51.0%)	142 (48.9%)	570 (100%)
Age of individuals(Mean ± S.D)	37.23±11.03 yrs*	35.10 ± 11.45 yrs*	36.55±11.75 yrs*

*p<0.01 was considered to be significant

Table 3. Number, percentage and age of individuals sensitive to different allergens

Type of allergens to which individuals were sensitized	Number of Patients (%)
Fungal allergens	73 (29.9%)
Age of Individuals (Mean± S.D)	39.25 ± 11.76*
Other allergens (HDM, pollen, insects, food)	135 (55.3%)
Age of Individuals (Mean± S.D)	35.46 ± 12.96*
Fungus + other allergens	36 (14.7%)
Age of Individuals (Mean± S.D)	34.96 ± 10.53*

*p<0.01 was considered to be significant

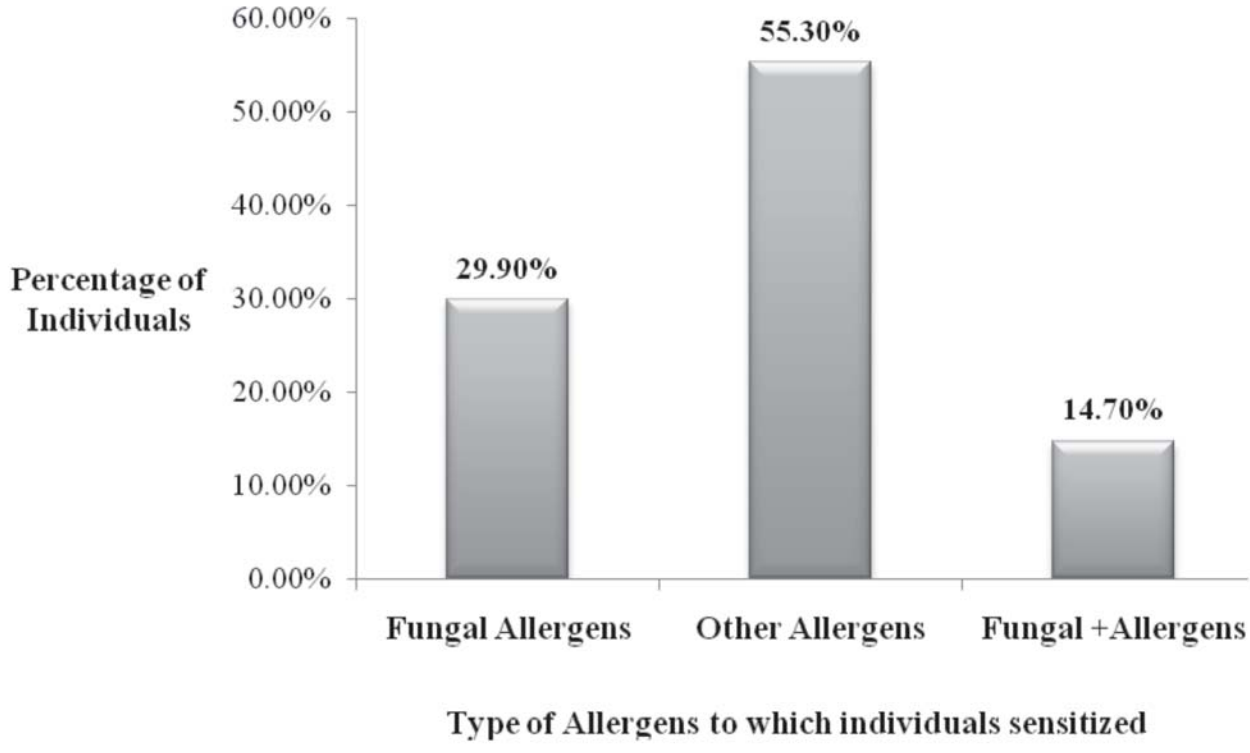

Fig 2. Graph showing percentage of individuals sensitive to different allergens

Table 4 (i) Number and percentage of individuals positive for only fungal allergens among various respiratory allergy patients

	Positive for fungal allergens only
Category	Number of individuals
AR	35 (47.9%)
AR with asthma	14 (19.17%)
AFS	24 (32.8%)
Total individuals (%)	73 (100%)

Table 4 (ii) Number and percentage of individuals with positive for fungal plus other allergens among various respiratory allergy patients

	Positive for fungal plus other allergens
Category	Number of individuals
AR	23(63.8%)
AR with asthma	10 (27.7%)
AFS	3 (8.3%)
Total (%)	36 (100%)

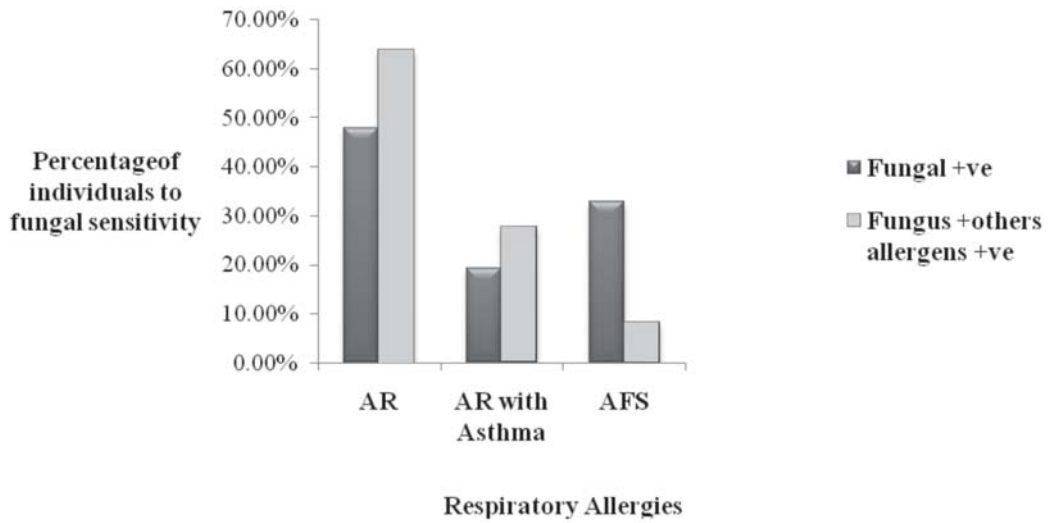

Fig 3. Fungal allergen sensitivity among individuals with various respiratory allergies

Table 5. Number of individuals sensitized to different type of fungi

Type of Fungi	AR	AR with Asthma	AFS	Total
Alternaria alternata	20	10	10	40
Aspergillus flavus	17	10	24	51
A. fumigatus	28	14	25	67
A. niger	16	6	10	32
A.tamarii	22	8	21	51
A.versicolor	14	7	6	27
Cladosporium	7	2	4	13
Candida	10	3	3	16
Mucor	6	2	9	17
Pencillium	11	3	7	21
Rhizopus	14	5	9	28
Trichoderma	6	0	2	8

Number of patients on whom fungal culture was done = 26

Fungal culture positive
20 patients (76.92%)

Fungal culture negative
6 patients (23%)

Aspergillus fumigatus: 11 patients (55%)

Aspergillus flavus: 8 (40%)

Aspergillus niger: 1 (5%)

Fig 4. Flow chart showing the results of fungal culture done on patients

Table 6. Comparative laboratory total IgE levels (IU/ml) among patients with various allergic conditions who were sensitive to all allergens

Category	Only Fungal +ve	Both (Fungal+others)	Others
AR	507.11±63.49*	689.97±71.56*	623.95±29.4*
	(367.37, 646.86)	(539.62, 840.32)	(565.92, 681.98)
AR with Asthma	601.14±75.88*	1114.41±230.90*	794.33±80.58*
	(406.67, 796.20)	(568.21, 1660.62)	(632.11, 956.55)
AFS	973.12±46.76*	2150.00±50.00**	
	(865.27,1080.97)	(1514.68, 2785.31)	

*p<0.01 was considered to be significant,

**p<0.05 was considered to be significant

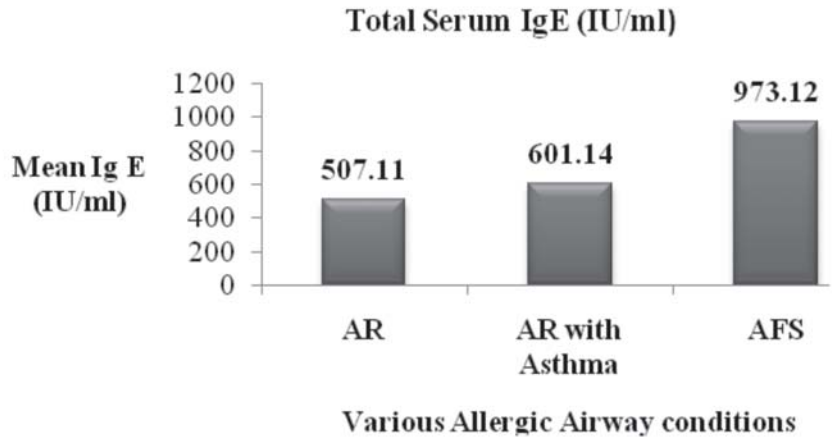

Fig 5. Comparative total IgE among patients with various allergic conditions who were positive to only fungal allergens

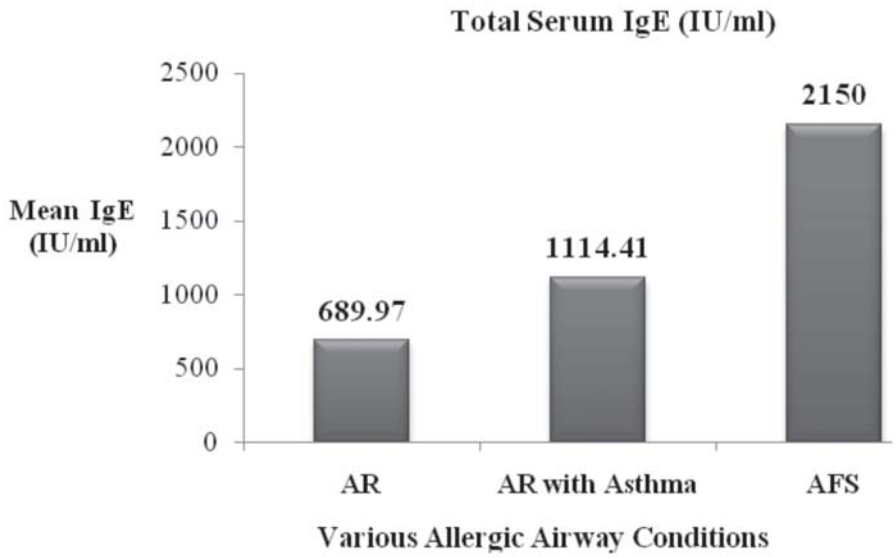

Fig 6. Comparative total IgE among patients with various allergic conditions who were sensitive to fungal plus other allergens

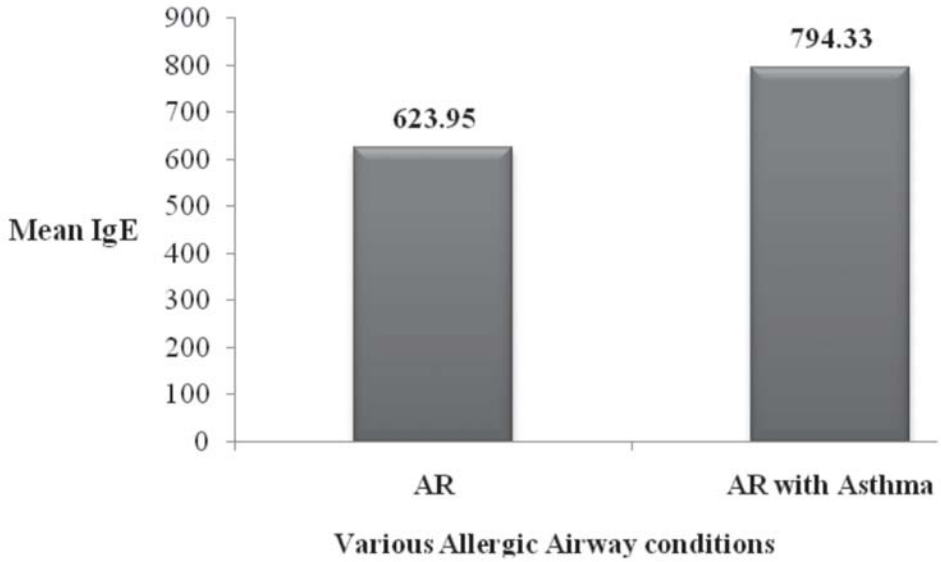

Fig 7. Comparative total IgE among patients with various allergic conditions who were positive to allergens other than fungus

Table 7. Comparative peripheral eosinophil count (%)) among patients with various allergic conditions who were sensitive to all allergens

Category	Only Fungal +ve	Both (Fungal+others)	Others
AR	6.58±1.21*	7.89±0.704*	7.15±0.840*
	(3.90, 9.25)	(6.41, 9.37)	(5.49, 8.81)
AR with Asthma	7.66±1.22*	9.25±1.63*	8.14±0.47*
	(4.50, 10.82)	(5.38, 13.11)	(7.19, 9.09)
AFS	11.44±1.63*	19.00±1.00**	
	(7.67, 15.21)	(6.29, 31.70)	

*p<0.01 was considered to be significant,

**p<0.05 was considered to be significant

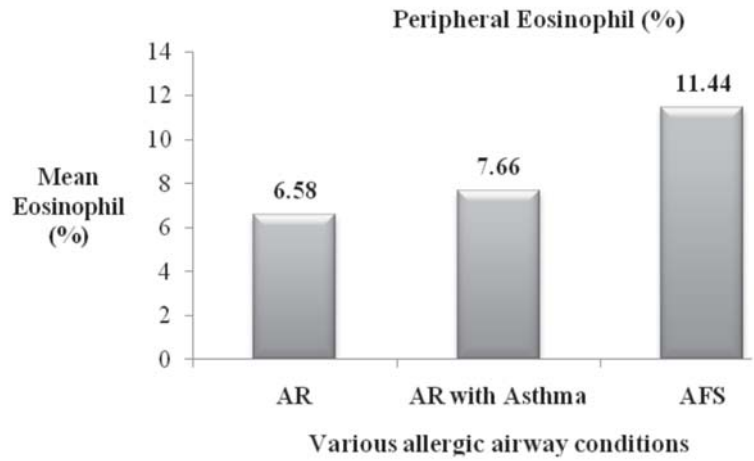

Fig 8. Comparative peripheral eosinophil (%) among patients with various allergic conditions who were positive only to fungal allergens

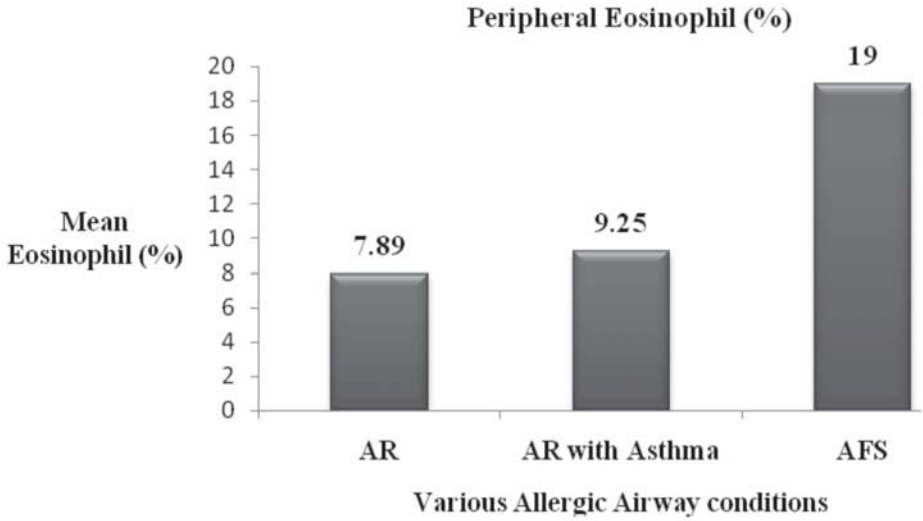

Fig 9. Comparative peripheral eosinophil (%) among patients with various allergic patients who were positive to fungal plus other allergens

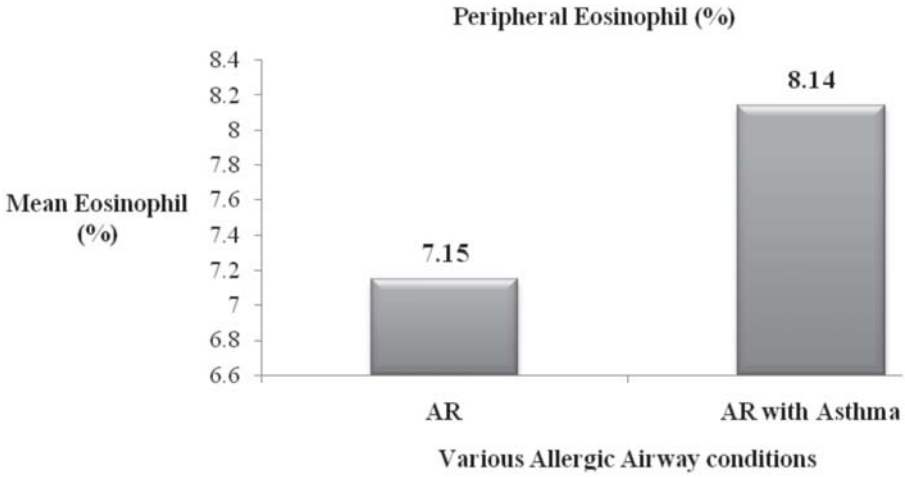

Fig 10. Comparative peripheral eosinophil (%) among patients with various allergic conditions who were sensitive to allergens other than fungus

DISCUSSION

Fungal antigens play an important role in the causation of respiratory allergies. Fungi disseminate their spores in the environment through air, water, insects, man and animals[11]. Air borne fungal spores have been implicated as causative factor in respiratory allergies particularly asthma[5]. Immunoglobulin E specific antigens (allergens) on air borne fungal spores induce type I hypersensitivity (allergic) respiratory reactions in sensitized subjects causing rhinitis or asthma[12]. Qualitative knowledge of these fungi in a given region is of great importance and concern because they can cause several respiratory diseases in man such as rhinitis and asthma when inhaled[11]. Lowry and Shaffer proposed multiple diagnostic criteria, including eosinophila, immediate skin reactivity or serum Ig E Antibodies to fungal antigens, nasal mucosal edema or polyposis[13].

The present study intended to explore the clinical profile of the individuals who were sensitized to different type of fungal allergens and find out the relationship between skin tests and laboratory markers total serum IgE, peripheral eosinophils) in different types of allergen sensitivity individuals among various respiratory allergy patients.

Air borne fungal spores occur widely and often in greater concentration than pollens. The prevalence of respiratory fungal allergy was found to be 20-30% of atopic individuals in the study conducted by Horner WE[12]. According to McClay *et al*, AFS is most common among adolescents and young adults; the mean age at diagnosis was 21.9 yrs and an incidence, equal in males and females was seen[14]. The group of patients aged 11 to 20 years had the highest incidence of mold sensitivity[15]. In the present study the most common age group with respiratory allergies was 37.03 yrs and the most common age group for mold sensitivity was 39.25 yrs.

The overall incidence of allergy to various allergens in our study was found significant. The incidence of allergy to fungal allergens in the study conducted by Erbek SS[16] was 38.8% in allergic patients. In our study the incidence to fungal allergen sensitivity was found to be quite significant (44%).

Skin test was found to be the most reliable method and available method for allergen sensitivity[17]. In studies in which the SPT was accepted as the gold standard, in vitro testing has proved less sensitive. Reported sensitivities have ranged from 74% [18] to 92.2%[19]. Present study showed that skin test positivity was 84.13% in properly selected cases. Among the total skin tests conducted in our study, 68.4% of them were intra dermal, 31.6% were skin prick tests. Our study has demonstrated that if the case has been selected properly after thorough history and

preliminary basic investigation, the incidence of positivity of skin tests appears to be quite high (84.13%). Among the individuals who were sensitive to allergens, 55% of the individuals were sensitized to allergens other than fungus, (HDM, pollen, insects, food, etc), 29.9% of individuals were sensitive to fungus only and 14.7% were sensitive to fungus plus other allergens. Therefore the present study has demonstrated that overall sensitivity to fungi was 44%.

Among the air borne fungi that spread air spores, important allergens of the world are *Aspergillus, Cladosporium, Alternaria, Penicillium* and *Dechslera*. They have been reported as the predominant organisms in warm, humid and dry climates [20]. A similar study was done by Mezzari *et al*[11] revealed a prevalence of air borne fungi in the city of Porto Alegre; the most predominant fungi found in the air of the city were: *Aspergillus, Cladosporium, Alternaria, Penicillium, Curvularia, Fusarium* and others. Aerobiological survey done in the city of Bangalore (South India) by Aghase and Vidya (1997) showed predominance of *Cladosporium, Alternaria, Aspergillus, Penicillium, Nigrospora, Helminthosporium, Cercospora* and *Curvularia*[21].

Skin tests conducted by Agahshe *et al*, were found to be positive for *Helminthosporium, Alternaria, Nigrospora and Cladosporium*[22]. In the present study the most identified fungal allergens were *Aspergillus, Alternaria, Cladosporium, Candida, Mucor, Penicillium, Rhizopus* and *Trichoderma.*

Grenn *et al* studied that allergens dispersed by airborne fungal spores play an important but poorly understood role in the underlying cause and exacerbation of asthma and rhinitis[23].

In our study, most of the individuals with respiratory fungal allergies had symptoms related to AR. Among the individuals who were sensitized only to fungus; 47.9% of the individuals suffered from AR, 19.17% suffered from AR with asthma followed by AFS (32.8%).

In cases of AR patients evaluated by skin tests, sensitivity was found more commonly for *A. fumigatus* followed by *A. tamari*. In cases of AR with asthma, the sensitivity was found to be more commonly for *A. fumigatus* followed by *A. flavus* and *Alternaria*. In cases of AFS it was *A. fumigatus* followed by *A. flavus* and *A. tamaraii*.

During skin tests, it was observed that the patients were sensitive to multiple fungal antigens. This could be due to cross reactivity between fungal antigens. A study in Finland showed the most common mold to induce occupational rhinitis was *A. fumigatus* [24]. An association between the immunoglobulin E (IgE) sensitization and exposure level was statistically significant. The mold that grew in conjunction with moisture damage was the leading cause of occupational rhinitis. The results of the study showed that the hierarchical structure of fungi based in IgE antibodies in sensitized individuals reflected the phylogenetic relationship[25].

According to Galante D *et al*[15], patients show elevated total IgE levels when persons were exposed fungal spores. The average serum IgE level was higher in patients with fungal spores. Present study showed that total IgE was found to be higher in individuals who were sensitive to fungal and other allergens followed by individuals who were sensitive to other allergens (except fungi) in all categories of respiratory allergy patients (AR, AR with asthma and AFS).

Among the individuals who showed positivity to fungus + other allergens, the total serum IgE was higher in cases of AFS and AR with asthma and it was also similar in the patients who were sensitive only to fungal allergens. Multiple elevations of fungal sIgE are adequate diagnostic evidence of these fungi when fungal cultures and histological examinations are negative in diagnosing AFS[26].

According to Erbek *et al*, there was no association found between fungal allergy, blood eosinophil, total immunoglobulin E levels and presence of polyps, or paranasal sinus computed tomography scores[16]. Our study demonstrated that the levels of peripheral eosinophil (%) followed same pattern as of IgE levels; it was higher in individuals who were sensitive to fungal and other allergens followed by individuals who were sensitive to other allergens (except fungi) in all categories of respiratory allergy patients (AR, AR with asthma and AFS).

In the study conducted by Braun H, 91.3% of fungal cultures were positive with chronic rhino sinusitis [27] and 96% were positive in the study conducted by Ponikau JU[28]. According to a review of english

literature performed in 1996 by Manning, 87% of fungal cultures were dematiaceous genera and 13% were Asperigillus[29]. In the present study, 76.92% of subjects had shown positivity in fungal culture and 23% were negative and most of the cases were positive for *Aspergillus fumigatus* (53%) followed by *A. flavus* (40%) and *A. niger* (5%). A report from India found that only *Aspergillus* species was identified in all patients with AFS from whom fungus was recovered and in south east it was *Curvularia* spp[30]. In our study *Aspergillus fumigatus* was the most common fungus (55%) identified in culture.

In Conclusion, the present study was intended to identify those fungi that are responsible for rhinitis and asthma in the population of south India. Proper history taking followed by skin tests, total/specific IgE in vitro tests, fungal culture in specific cases are helpful in the diagnosis.

Fungal sensitivity that was observed in the study population was mainly for *Aspergillus*, followed by *Alternaria*. Sensitivity to multiple fungal antigens in a single individual observed during skin tests could be due to cross reactivity between fungal antigens. Diagnosis and immunotherapy of allergy to fungi require well characterized or standardized extracts that contains the relevant allergens of the appropriate fungus. Complex allergen extracts presently used in diagnosis of fungal allergy are to be substituted by single, perfectly standardized components for clinical testing. Recombinant fungal allergens might create new perspectives in diagnosis and therapy of fungal allergy. Aerobiological studies and control of environmental factors can reduce the burden of allergy in human beings. More such studies from India may help in better understanding of the condition which can lead to proper diagnosis and management.

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