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Research Article

ROLE OF ASPERGILLUS SENSITIZATION ON DISEASE SEVERITY IN PATIENTS WITH BRONCHIAL ASTHMA AND ITS CONSEQUENCES ON ITS PREVALENCE

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A B S T R A C T

Identification of Aspergillus sensitization in patients with bronchial asthma and its clinical significance. So this study is planned to find out the prevalence of Aspergillus sensitization in patients with bronchial asthma and to evaluate the impact of Aspergillus sensitization on disease severity.

This is a perspective cross-sectional study conducted between Sept 2016 to Sept 2017 in the Department of Pulmonary Medicine, Career Institute of Medical Sciences, Lucknow. The study was approved by the institutional ethics committee and written consent was taken from all patients who were enrolled in the study. This cross-sectional observational study was aimed at studying the basic differences in disease characteristics and the severity of bronchial asthma between aspergillus sensitive patients and aspergillus non-sensitive patients. The ancillary findings include Prevalence of Aspergillus sensitization, Proportion of patients with Aspergillus. The prevalence of Aspergillus sensitization was estimated previously by several studies. It was found to be a minimum of 33%, 28%, 35.1%. The various factors responsible for the varied prevalence of Aspergillus sensitization were differences in environment and exposure to allergens, differences in methods of diagnosing fungal sensitization. In our study, both skin prick test and specific IgE were used for diagnosing the fungal sensitization which reduces the discordance of results between the two.

INTRODUCTION

Bronchial Asthma is one of the common chronic respiratory illnesses worldwide with a global disease burden affecting about 300 million [1, 2] populations. It affects 5-10% [3] of the population even in developed countries. India constitutes about one-tenth of the global disease burden. An estimated 7 million children are affected by this illness.

The pathophysiology of asthma is complex and involves airway inflammation, bronchial hyper-responsiveness and intermittent airflow obstruction. Airway inflammation is identified as the core pathology triggering the cascade all-around. Recent studies reveal the involvement of multiple pathways getting funnelled into a common endpoint, being airway inflammation. But quantifying airway inflammation is not practical as of now. Thus, phenotyping of asthma has started gaining momentum with researches targeting its endotype leading to a particular phenotype.

Airway inflammation is the result of Th2-mediated response which leads to classical symptoms of the disease.

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Yet it has been proven clearly that about 50% of asthma including severe asthma patient's show less evidence of Th2 mediated response[4]. The current focus is shifted towards phenotypic diagnosis; severe asthma is one such phenotype. Fungus-related asthma is one of the most studied subtypes of severe asthma.

Airway hyperresponsiveness or bronchial hyperreactivity in asthma is an exaggerated response to numerous exogenous and endogenous stimuli. The most important endogenous stimuli are considered to be fungal antigens of Aspergillus species. The positive skin reactions to Aspergillus fumigatus in atopic asthmatics is 10 to 20% [5]. But a causal relationship is yet to be established. A separate entity termed 'Severe asthma with fungal sensitivity' with milder allergic reactions to fungal aeroallergens, when compared to allergic bronchopulmonary aspergillosis, has fungal sensitisation as the starting point of pathogenesis. This study aims at studying the various characteristics of bronchial asthma in relation to fungal sensitisation. Fungal allergy Immune-mediated inflammatory response to a fungus sometimes leading to tissue damage.

Fungal sensitisation Immune-mediated response to a fungus, without evidence of inflammation or tissue damage, usually documented by an elevated fungal-specific Immunoglobulin E(IgE). Fungal colonisation Growth of fungus in the

respiratory tract and development into fungal hyphae and elaborating allergens.

Identification of Aspergillus sensitization in patients with bronchial asthma and its clinical significance. So this study is planned to find out the prevalence of Aspergillus sensitisation in patients with bronchial asthma and to evaluate the impact of Aspergillus sensitization on disease severity.

MATERIAL & METHODS

This is a perspective cross-sectional study conducted between Sept 2016 to Sept 2017 in the Department of Pulmonary Medicine, Career Institute of Medical Sciences, Lucknow. The study was approved by the institutional ethics committee and written consent was taken from all patients who were enrolled in the study. Patients will be included in the study if they are aged 18 years or more and meet either or both of the following criteria for the diagnosis of bronchial asthma: History of recurrent or episodic attacks of chest tightness, wheezing, breathlessness and cough (especially nocturnal). The obstructive pattern on spirometry with or without the presence of bronchodilator reversibility. (FEV1/FVC< 0.75 with reversibility increase in FEV1 of >12% and >200 mL from baseline, 10–15 minutes after 200 -400 mcg albuterol or equivalent). Age more than 65 years, Diagnosis of ABPA or chronic obstructive pulmonary disease, Pregnancy, Other immunosuppressive states such as chronic liver disease, chronic renal failure, uncontrolled diabetes mellitus, chronic heart failure, immunosuppressive drugs other than glucocorticoids for controlling asthma, Failure to give informed consent were excluded from the study.

A comprehensive clinical history was taken for all patients who also underwent detailed clinical evaluation. Comprehensive evaluation includes: age, gender, occupation, residence, anthropometric details (height, weight, body mass index), smoking history, family history of asthma /allergy, exposure to animals (cattle, birds, cats, dogs), cardinal symptoms of bronchial asthma (breathlessness, chest tightness, wheeze, cough), co-morbidities (diabetes mellitus, hypertension, obesity, hypothyroidism, gastroesophageal reflux disease, depression, voice changes), history of nasal atopy to dust, smoke, perfumes, cold exposure and drug allergy.

Aspergillus sensitization tests*:* Aspergillus sensitisation was tested initially with skin prick test (SPT) using commercially available allergen obtained from 'Allure pharma' and was graded using the following grading 1+,2+,3+,4+,5+ respectively for 0 -3 mm,3 – 5 mm,6-8 mm,9 -11 mm,> 11 mm wheal diameter [6].Aspergillus-specific IgE was done using commercial Immuno CAP system with 0.35kUA/L as a reference for positive result[7]

Asthma control test[8]: The ACT is a validated, self-administered questionnaire with five items that have been developed as an easy method for patients and clinicians to assess symptoms (daytime and nocturnal), use of rescue medications and the effect of asthma on daily functioning. Each item includes five response options corresponding to a five-point Likert-type rating scale. In scoring the ACT, responses for each of the five items are summed to yield a score ranging from 5 (poor control of asthma) to 25 (complete control of asthma) An ACT score of 19 or less is suggestive of difficulty in controlling asthma

GINA (Global initiative for asthma) symptom control[9]*:* Symptom control was assessed using GINA symptom control questionnaire after adhering to treatment for at least 1 month and were graded well-controlled, partly or uncontrolled.

Statistical analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 Statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

RESULTS

Table 1 Distribution of Study Population according to Aspergillus sensitivity

Group	Description	No. of patients	Percentage
Group I	Aspergillus sensitive	20	35.09
Group II	Aspergillus negative	37	64.91
	Total	57	100.00

Out of 57 patients enrolled in the study, 20 (35.09%) were found to be Aspergillus sensitive were classified as Group I while rest 37 (64.91%) were found to be Aspergillus negative were classified as Group II.

Table 2 Comparison of Demographic Variables

Variables	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
Age Group (years)						
≤20	3	15.00	7	18.92	10	17.54
21-40	15	75.00	21	56.76	36	63.16
>40	2	10.00	9	24.32	11	19.30
	χ^2=2.178(df=2); p=0.337					
Min-Max (Median)	18-42 (27.00)		18-74 (35.00)		18-74 (30.00)	
Mean±SD	27.65±7.32		33.78±12.49		31.63±11.28	
Gender						
Female	12	60.00	23	62.16	35	61.40
Male	8	40.00	14	37.84	22	38.60
	χ^2=0.026(df=1); p=0.873					
Habitat						
Rural	8	40.00	13	35.14	21	36.84
Urban	12	60.00	24	64.86	36	63.16
	χ^2=0.132(df=1); p=0.716					

Age of patients enrolled in the study ranged from 18-74 years and median age of patients was 30 years, range of age among patients of Group I was 18-42 (median 27) years and among Group II was 18-74 (median 35) years. Mean age of patients of Group I (27.65±7.32 years) was found to be lower than that of Group II (33.78±12.49 years). Majority of overall patients as well as enrolled in Group I and Group II were aged 21-40 years (63.16%, 75.00% and 56.76%). Proportion of patients of Group II was higher as compared to that of Group I in age groups ≤20 years (18.92% vs. 15.00%) and 41-50 years (24.32% vs. 10.00%), but difference in age of patients of both the groups was not found to be statistically significant. Majority of overall (61.40%) as well as patients enrolled in Group I (60.00%) and Group II (62.16%) were females and rest of the patients were males. Difference in gender of patients of both the groups was not found to be statistically significant (p=0.873). Majority of overall (63.16%) as well as patients enrolled in Group I (60.00%) and Group II (64.86%) were from urban areas and rest of the patients were from rural areas. Difference in Habitat of patients of both the groups was not found to be statistically significant (p=0.716).

Table 3 Comparison of Occupation

Variables	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
Student	6	30.00	8	21.62	14	24.56
Teacher/Staff Nurse	2	10.00	6	16.22	8	14.04
Shopkeeper	2	10.00	3	8.11	5	8.77
Housewife	7	35.00	14	37.84	21	36.84
Farmer	1	5.00	3	8.11	4	7.02
Other Skilled Laborers	2	10.00	3	8.11	5	8.77
χ^2=1.042(df=5); p=0.959						

Table 4 Comparison of Nutritional Status

Nutritional Status (BMI)	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
Underweight	2	10.00	3	8.11	5	8.77
Normal	11	55.00	22	59.46	33	57.89
Overweight	6	30.00	11	29.73	17	29.82
Obese	1	5.00	1	2.70	2	3.51
χ^2=0.293(df=3); p=0.961						
BMI : Min-Max (Median)	14.5-30.3 (22.80)		16.0-31.1(22.00)		14.5-31.1(22.20)	
BMI: Mean±SD	23.12±4.32		23.00±3.69		23.04±3.89	

BMI of patients enrolled in the study ranged from 14.5-31.1 kg/m^2 in overall, 14.5-30.3 kg/m^2 among Group I and 16.0-31.1 kg/m^2 among patients of Group II. Mean BMI of patients of Group I (23.12±4.32 kg/m^2) was found to be slightly higher than that of Group II (23.00±3.69 kg/m^2).Difference in nutritional status of patients of above two groups was not found to be statistically significant (p=0.961).

Table 5 Comparison of Habit of Smoking

Variables	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
Smoker(Current and ex-smoker)	2	10.00	1	2.70	3	5.26
Non-Smoker	18	90.00	36	97.30	54	94.74
χ^2=1.386(df=1); p=0.239						

Majority of patients enrolled in the study were non-smokers (n=54; 94.74%) and rest 3 (5.26%) were smokers or ex-smokers. Though proportion of smokers was higher among patients of Group I (10.00%) as compared to that in Group II (2.70%) but this difference was not found to be statistically significant (p=0.239).

Table 6 Comparison of Duration of Illness (years)

Group	No. of patients	Min.	Max	Median	Mean	S.D.
Group I	20	0.50 (6 m)	20.00	4.50	5.93	5.71
Group II	37	0.25 (3 m)	30.00	5.00	7.00	6.75
Total	57	0.25 (3 m)	30.00	5.00	6.63	6.37

't'=0.607; p=0.546 (NS)

Duration of illness among patients enrolled in the study ranged from 3 months to 2.5 years among overall and Group II patients while that in Group I was 6 months to 20 months. Mean duration of illness was higher in patients of Group II (7.00±6.75 months) as compared to Group I (5.93±5.71 months). Difference in mean duration of illness of patients of Group I and Group II was not found to be statistically significant (p=0.546).

Table 7 Comparison of Presenting Symptom and Seasonal Variability

Symptoms	Total (N=57)	Group I (n=20)		Group II (n=37)		Statistical significance	
		No.	%	No.	%	χ^2	P
Breathlessness	52	18	90.00	34	91.89	0.058	0.810
Cough	55	19	95.00	36	97.30	0.202	0.653
Chest tightness	36	12	60.00	24	64.86	0.132	0.716
Wheezing	44	15	75.00	29	78.38	0.084	0.772
Seasonal variability	36	10	50.00	26	70.27	2.292	0.130

Comparison of Presenting Symptom and Seasonal Variability

Cough (n=55; 96.49%), Breathlessness (n=52; 91.23%) and Wheezing (n=44; 77.19%) were most common presenting symptoms among our study population while Chest tightness (n=36; 63.16%) and Seasonal variability (n=36; 63.16%) were less common presenting symptoms.

For all the above presenting symptoms, incidence was higher among Group II as compared to Group I i.e. Breathlessness (91.89% vs. 90.00%), Cough (97.30% vs. 95.00%), Chest tightness (64.86% vs. 60.00%), Wheezing (78.38% vs. 75.00%) and Seasonal variability (70.27% vs. 50.00%), but none of these differences were found to be statistically significant.

Table 8 Comparison of Exposure to Known Allergens

	Total (N=57)	Group I (n=20)		Group II (n=37)		Statistical significance	
		No.	%	No.	%	χ^2	P
Dust	39	13	65.00	26	70.27	0.167	0.683
Smoke	38	13	65.00	25	67.57	0.039	0.844
Cold exposure	6	1	5.00	5	13.51	0.999	0.318
Perfumes	7	2	10.00	5	13.51	0.149	0.700
Peanuts	1	0	0.00	1	2.70	0.550	0.458
Drug (Ibuprofen) Allergy	1	0	0.00	1	2.70	0.550	0.458
Exposure to animals (Cow, Buffalo, Goat)	20	8	40.00	12	32.43	0.326	0.568

Comparison of Exposure to Known Allergens

Among our study population exposure to dust (n=39; 68.42%) and smoke (n=38; 66.67%) and animals like cow, buffalo and goat (n=20; 35.09%) were common. Exposure to perfumes (n=7; 12.28%), cold (n=6; 10.53%), Peanuts (n=1; 1.75%) and Ibuprofen (n=1; 1.75%) was less common.

Proportion of patients of Group II was higher as compared to Group I for all the known allergens – Dust (70.27% vs. 65.00%), Smoke (67.57% vs. 65.00%), Cold (13.51% vs. 5.00%), Perfumes (13.51% vs. 10.00%), Peanuts (2.70% vs. 0.00%), Drugs like Ibuprofen (2.70% vs. 0.00%) except exposure to pets which was higher among patients of Group I (40.00%) as compared to Group II (32.43%). Difference in exposure to none of the above known allergens among patients of Group I and Group II were found to be statistically significant (p>0.05 each).

Table 9 Comparison of Associated Illness

	Total (N=57)	Group I (n=20)		Group II (n=37)		Statistical significance	
		No.	%	No.	%	χ^2	P
History of nasal atopy	40	13	65.00	27	72.97	0.394	0.530
Diabetes mellitus	2	1	5.00	1	2.70	0.202	0.653
Hypertension	1	0	0.00	1	2.70	0.550	0.458
Gastroesophageal reflux disease	0	0	0.00	0	0.00	–	–
Obesity	2	1	5.00	1	2.70	0.202	0.653
Anxiety	0	0	0.00	0	0.00	–	–
Depression	0	0	0.00	0	0.00	–	–
Hypothyroidism	5	3	15.00	2	5.41	1.493	0.222
Family history	21	8	40.00	13	35.14	1.832	0.176
Other*	3	1	5.00	2	5.41	0.004	0.948

*Infertility, Psoriasis, Sinus surgery

Out of 57 patients, 40 (70.18%) were suffering from nasal atopy, 2 (3.51%) were diabetic, 1 (1.75%) had hypertension, 2 (3.51%) obese, 5 (8.77%) were hyperthyroid, 21 (36.84%), and three patients (1 each) were suffering from infertility, Psoriasis and Sinus surgery. Anxiety, Depresssion or gastroesophageal reflux were not found in any of the patients enrolled in the study.

Difference in incidence of none of the above associated illnesses among patients of Group I and Group II was found to be statistically significant.

Table 10 Associated Allergic rhinitis

Variables	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
AR with BA	12	60.00	28	75.68	40	70.18
BA	8	40.00	9	24.32	17	29.82
χ^2=1.524(df=1); p=0.217						

Majority of patients (overall as well as Group I and Group II – 70.18%, 60.00% and 75.68%) were diagnosed of Allergic rhinitis with bronchial asthma while rest of the patients was diagnosed of bronchial asthma. Though proportion of patients diagnosed as Bronchial asthma was higher among Group I (40.00%) as compared to Group II (24.32%) but this difference was not found to be statistically significant.

Table 11 Comparison of Clinical Findings

Clinical Findings	Total (N=57)	Group I (n=20)		Group II (n=37)		Statistical significance	
		No.	%	No.	%	χ^2	P
Rhonchi	40	16	80.00	24	64.86	1.421	0.233
Crepts	1	1	5.00	0	0.00	1.883	0.170

On Clinical examination 40 (70.18%) patients were diagnosed abnormalities of Rhonchi and 1 (1.75%) of Crepts. Abnormalities of Rhonchi were found in higher proportion of patients of Group I (80.00%) as compared to Group II (64.86%) but this difference was not found to be statistically significant. Crepts were found in 1 (5.00%) patients of Group I only.

Table 12 Comparison of X-ray Findings

X-ray Findings	Total (N=57)	Group I (n=20)		Group II (n=37)		Statistical significance	
		No.	%	No.	%	χ^2	P
Hyperinflation	4	1	5.00	3	8.11	0.192	0.661
Increased markings	2	1	5.00	1	2.70	0.202	0.653
Bronchiectasis	0	0	0.00	0	0.00	–	–

Hyperinflation (n=4; 7.02%) and increased markings (n=2; 3.51%) were observed on X-ray of patients enrolled in the study. Bronchiectasis was not observed in any of the X-ray findings patients enrolled in the study. Hyperinflation was found in higher proportion of patients of Group II (8.11%) as compared to Group I (5.00%) but this difference was not found to be statistically significant.

Increased marking were observed in 1 patient each from Group I and Group II, though proportion of patients of Group I was higher as compared to Group II but this difference was not found to be statistically significant.

Table 13 Comparison of High Resolution Computed Tomography (HRCT) Findings

	Total (N=57)	Group I (n=20)		Group II (n=37)		Statistical significance	
		No.	%	No.	%	χ^2	P
Bronchiectasis	10	7	35.00	3	8.11	6.490	**0.011**
Mucus Plugging	2	1	5.00	1	2.70	0.202	0.653
Emphysema	10	4	20.00	6	16.22	0.128	0.720
Bronchial wall thickneing	4	2	10.00	2	5.41	0.420	0.517
Others*	9	6	30.00	3	8.11	4.679	**0.031**

*Cyst, Fibrosis, Focal ground glass opacity, Nodules & Ground glass opacity, Patchy ground glass opacity

Incidence of abnormalities exposed by HRCT findings was higher among Group I as compared to Group II. Significantly higher proportion of patients of Group I as compared to Group II were found for bronchiectasis (35.00% vs. 8.11%) and Other findings including cyst, fibrosis, ground glass opacity, nodules & ground glass opacity, patchy ground glass opacity (30.00% vs. 8.11%).Incidence was higher among patients of Group I and Group II of Mucus plugging (5.00% vs. 2.70%), Emphysema (20.00% vs. 16.22%) and bronchial wall thickening (20.00% vs. 16.22%) but these differences were not found to be statistically significant.

Table 14 Findings of Skin Prick Test

	No.	%
A. fumigatus		
1+	1	5.00
2+	5	25.00
3+	2	10.00
4+	1	5.00
Negative	11	55.00
A. flavus		
2+	3	15.00
3+	5	25.00
4+	2	10.00
Negative	10	50.00
A. niger		
1+	2	10.00
2+	7	35.00
Negative	11	55.00

Table 15 Comparison of Hematological Variables

Variable	Group I (n=20)		Group II (n=37)		Student 't' test	
	Mean	SD	Mean	SD	't'	'p'
Hemoglobin	12.97	1.50	12.80	1.41	0.419	0.677
TLC	7963.00	2207.69	7788.92	1788.73	0.323	0.748
Eosinophil %	6.40	3.94	5.73	4.32	0.576	0.567
AEC	558.90	438.00	490.35	486.87	0.525	0.602

No significant difference in hematological variables Hb, TLC, Eosinophil counts and AEC of patients of Group I and Group II were found.

Table 16 Comparison of Spirometry Findings

Variable	Group I (n=19)		Group II (n=36)		Student 't' test	
	Mean	SD	Mean	SD	't'	'p'
FEV1 (% pred.)	64.23	25.37	59.94	18.94	0.708	0.482
FVC (% pred.)	71.36	22.92	68.01	16.76	0.620	0.538
FEV1/FVC (pre)	73.61	7.74	74.64	11.53	-0.349	0.729
FEV1/FVC (post)	76.93	9.45	78.06	11.03	-0.380	0.705

No significant difference in spirometry findings – FEV1 (% predicted), FVC (% predicted), and FEV1/FVC (pre) and FEV1/FVC (post) of patients of Group I and Group II were found.

Table 17 Comparison of Total IgE

Total IgE	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
<500 UI/ml	7	35.00	13	35.14	20	35.09
501-1000 UI/ml	4	20.00	8	21.62	12	21.05
>1000 UI/ml	9	45.00	16	43.24	25	43.86
χ^2=0.025(df=2); p=0.987						
Min-Max (Median)	141-16543 (737.5)		104-12976 (780)		104-16543 (753)	
Mean±SD	2220.95±4380.01		1373.59±2132.65		1670.91±3098.28	
't'=0.985; p=0.329 (NS)						

Difference in IgE levels among patients of Group I and Group II was not found to be statistically significant. Though proportion of higher IgE levels >1000 UI/ml was higher among patients of Group I (45.00%) as compared to Group II (43.24%) and of lower IgE levels was higher among Group II as compared to Group I, <500 UI/ml (35.14% vs. 35.00%) and 501-1000 IU/ml (21.62% vs. 20.00%), but this difference was not found to be statistically significant. Though mean Total IgE levels of Group I (2220.95±4380.01UI/ml) was found to be higher than that of Group II (1373.59±2132.65 UI/ml) but this difference was not found to be statistically significant (p=0.329).

Table 18 Comparison of ACT Score

ACT Score	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
≤19	2	10.00	8	21.62	10	17.54
>19	18	90.00	29	78.38	47	82.46
χ^2=1.212(df=1); p=0.271						
Min-Max (Median)	18-24 (22.50)		15-25 (24.00)		15-25 (23.00)	
Mean±SD	22.15±1.81		22.46±2.61		22.35±2.35	

Chart 17: Comparison of ACT Score

ACT score of >19 was found in majority of overall (8246%) as well as Group I (90.00%) and Group II (78.38%) patients, rest of the patients had ACT score ≤19. Difference in ACT score of patients of Group I and Group II was not found to be statistically significant (p=0.271).

Table 19 Comparison of Previous Hospitalization

H/o Hospitalization	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
Previously Hospitalised	3	15.00	4	10.81	7	12.28
No Previous Hospitalised	17	85.00	33	89.19	50	87.72
χ^2=1.152(df=2); p=0.562						

No previous hospitalization history was found in majority of overall (87.72%) as well as Group I (85.00%) and Group II (89.19%) patients, rest of the patients had history of previous hospitalization. Difference in previous hospitalization history of patients of Group I and Group II was not found to be statistically significant (p=0.562).

Table 20 Comparison of Exacerbations in previous year

Exacerbations during previous year	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
<5	7	35.00	20	54.05	27	47.37
5-10	3	15.00	8	21.62	11	19.30
11-30	9	45.00	8	21.62	17	29.82
>30	1	5.00	1	2.70	2	3.51
χ^2=3.864(df=3); p=0.276						
Min-Max (Median)	2-50 (12.00)		1-50 (9.00)		1-50 (10.00)	
Mean±SD	14.88±12.20		10.32±10.46		11.98±11.20	

Number of exacerbations during previous year among overall and Group II patients ranged from 1-50 while that among Group I patients was 2-50. Mean number of exacerbation among patients of Group I (14.88±12.20) was higher as compared to that of Group II (10.32±10.46). Proportion of patients of Group II was higher for lower number of exacerbations i.e. <5 (54.05% vs. 35.00%) and 5-10 (21.62% vs. 15.00%) while proportion of patients of Group I was higher as compared to Group II for higher number of exacerbations i.e. 11-30 (45.00% vs. 21.62%) and >30 (5.00% vs. 2.70%). Difference in number of exacerbation during previous year among patients of Group I and Group II was not found to be statistically significant (p=0.276).

Table 21 Comparison of Symptom control

Symptoms	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
Uncontrolled	9	45.00	7	18.92	16	28.07
Partly Controlled	1	5.00	7	18.92	8	14.04
Well Controlled	10	50.00	23	62.16	33	57.89
χ^2=5.270(df=2); p=0.072						

Symptoms were well controlled in majority of the patients (57.89%), partly controlled in 14.04%. Uncontrolled symptoms were observed in only 28.07% patients. Proportion of symptoms with Uncontrolled symptoms was higher among patients of Group I (45.00%) as compared to Group II (18.92%) while proportion of patients of Group II was higher as compared to Group I having Partly controlled (18.92% vs. 5.00%) and Well controlled (62.16% vs. 50.00%) symptoms.

Table 22 Comparison of Symptom control (uncontrolled and partly controlled merged)

Symptoms	Group I (n=20)		Group II (n=37)		Total (N=57)	
	No.	%	No.	%	No.	%
Uncontrolled/ Partly controlled	10	50.00	14	37.84	24	42.11
Well Controlled	10	50.00	23	62.16	33	57.89
χ^2=0.788(df=1); p=0.375						

Proportion of Well controlled symptoms was higher among patients of Group II (62.16%) as compared to Group I (50.00%) and in rest of the patients symptoms were Uncontrolled or partly controlled. Difference in control of symptoms of patients of above two groups was not found to be statistically significant

DISCUSSION

This cross-sectional observational study was aimed at studying the basic differences in disease characteristics and the severity of bronchial asthma between aspergillus sensitive patients and aspergillus non-sensitive patients. The ancillary findings include Prevalence of Aspergillus sensitization, Proportion of patients with Aspergillus sensitization and severe asthma, Spirometry and IgE level differences between the two groups, Symptom control differences between the two groups. Out of the total of 57 patients, 35.09% were aspergillus sensitized individuals (20/57) which are the prevalence of Aspergillus sensitization in patients with bronchial asthma. The prevalence of Aspergillus sensitization was estimated previously by several studies. It was found to be a minimum of 33%[10], 28%[11], 35.1%[12]. The various factors responsible for the varied prevalence of Aspergillus sensitization were differences in environment and exposure to allergens, differences in methods of diagnosing fungal sensitization. In our study, both skin prick test and specific IgE were used for diagnosing the fungal sensitization which reduces the discordance of results between the two[10]

***Age*:** Mean age of patients with Aspergillus sensitization was found to be lower than aspergillus non-sensitised individuals (27.65 yrs VS 33.78 yrs).Though this was not statistically significant, this can be explained in a way that a fungal sensitization is an event which starts early in life in predisposed individuals. The disease models for fungal sensitization are given below as proposed by Denning *et al*[10] Fungal colonization is the first step in the process of sensitization. For the fungi to be persistent in the bronchial tree leading to germination and elaboration of allergens, it requires a conducive environment eg. an asthmatic lung.60% of asthmatics sensitized to Asf show growth in their sputum culture even in the first sample. All these describe clearly that fungal sensitization is an early age process. Early exposures to moulds significantly increase the risk for asthma in later life[13].

Occupation

ABPA presenting in relation to occupation was documented in few instances like in compost workers[13] and brewers of soy sauce and bean paste[14].But as the habitat of aspergillus suggests, exposure to fungus is universal with sensitisation in a proportion of patients. In our study, such a unique occupation was not observed and no such relationship was found.

Body mass index (BMI)

Increased BMI and an increase in the allergic phenotype of bronchial asthma has been documented in many studies[15]. Though it was significantly associated with bronchial hyper-reactivity, no association was drawn between functional parameters and BMI. But as far as fungal sensitisation is concerned there are no specific confirmatory studies relating fungal sensitisation directly with BMI. In our study too, there was no significant relationship between BMI and fungal sensitisation.

Duration of illness

Duration of illness in both the groups were similar with a mean of 5.93 years in aspergillus sensitive individuals and 7 years in aspergillus non-sensitive individuals which were previously confirmed in the study by Ritesh Agarwal *et al*[16].

Symptoms of bronchial asthma

The predominant symptom was a cough (96.4%) followed by breathlessness (91.2%), wheezing(77.1%) and the least common symptom was chest tightness(63.1%) which was similar in both the groups. Seasonal variation was present in 50% of Aspergillus sensitised individuals and 70.27% of non-sensitive individuals.

Known allergen exposure

Dust (68.4%) and smoke (66.6%) were the commonest allergens that could be identified by the patients as they could recollect a temporal relation with an episode. Perfumes (1.2%) and cold exposure (1%) were other allergens reported by the patients.31% of the patients were not able to identify any known allergen. Exposure to animals was observed in 35.08% which was closely similar in both groups.

Co-existing illness

Nasal atopy was seen in 70.1% of patients similar in both groups (65% and 72.9% in sensitive and non-sensitive individuals respectively). Family history was present in 21/57 i.e., 36.8% of patients. Allergic rhinitis was associated with 70.18% of patients.

Radiological findings in asthma

It is well known that airway abnormalities are common in bronchial asthma. The abnormality that is of special importance in aspergillus sensitive individuals is bronchiectasis, as a severe form of Aspergillus hypersensitivity leads to ABPA in which bronchiectasis is classical. As Aspergillus sensitisation is the first step in both SAFS and ABPA, the search for bronchiectasis in sensitised individuals is of prime importance. Bronchiectasis is seen in 9.1% of asthma patients[17]. Airway abnormalities are common in patients with severe asthma[18].In previous studies too, Bronchiectasis was found to be common in aspergillus sensitive individuals[19].In our study,7/20 patients in the sensitised group showed bronchiectasis whereas 3/37 patients in the non-sensitised group had bronchiectasis (p=0.011). The other significant finding between 2 groups was nodules, ground glass opacity and fibrosis which was common in sensitised individuals.

Spirometry findings

% predicted FEV1 in aspergillus sensitised individuals is 64.23 which is higher than 59.94 in Aspergillus. Menzies D *et al*[19] concluded that post-bronchodilator (BD) FEV1/FVC in aspergillus sensitised individuals were worse than non-sensitised individuals. In this study mean post-BD FEV1/FVC was 76.93 in sensitised individuals and 78.06 in non-sensitised individuals. This is in accordance with the study by Agbetile J *et al*[20].

Immunoglobulin e (IgE)

Total IgE > 1000 IU/mL is an important criterion in diagnosing ABPA. Total IgE less than the cut-off value in ABPA is a rare inactive disease. So apparently IgE must be correlating with Aspergillus sensitisation but previous studies prove otherwise. Total IgE is not significantly related to lung function in terms of spirometry indices or radiological abnormalities. It is not a useful biomarker for lung damage due to fungal allergy[21]

Raised total IgE is not only specific to asthma and it points only to an allergic cause. Though total IgE is reproducible and low cost, it is neither useful in asthma diagnosis nor in follow-up(except guiding omalizumab treatment). Sensitisation to perennial aeroallergens in the form of specific IgE is related to the increase in the severity of asthma[49].In this study, there was no significant relation between IgE and Aspergillus sensitisation with mean IgE of 2220.95 IU/mL in sensitized individuals and 1373.59 in non-sensitised individuals.

Asthma severity and Aspergillus sensitization

This is discussed under 3 parameters: Asthma control test (ACT), Hospitalisations and exacerbations, GINA symptom control

Asthma control test (ACT): In the study by Ritesh Agarwal *et al*[16], sensitized individuals when subjected to ACT showed increased symptoms during the night while other domains showed no difference. In the subjective parameter of rating of asthma control by patients, most patients rated their control to be better than what actually was, which was revealed by ACT>19 in 82.46%(discordant with GINA symptom control)Yet fungal sensitisation had no significant effect on ACT scores.

Hospitalisations & exacerbations: O'Driscoll B *et al*[22] concluded that mould sensitization may be associated with severe asthma attacks requiring hospital admission with maximum admissions occurring during mould spore season. The above study showed that there were increased hospital admissions in sensitized individuals and there was a temporal association between admission and spore season.

The severity of asthma is obviously related with more exacerbations and admissions.15% of 20 sensitized patients were already hospitalized whereas 10.81% of 37 non-sensitized patients were hospitalised.7/20(35%) sensitized individuals had less than 5 exacerbations in the previous year whereas 20/37 non-sensitized patients (54.05%) had less than5 exacerbations in the previous year. The proportion of sensitized individuals having <5 exacerbations per year was less when compared to non-sensitized individuals and > 30 exacerbations/year was present in 1/20(5%) of sensitized individuals was higher than1/37(2.7%) of non-sensitized patients.

Gina symptom control: Uncontrolled symptoms (9/20) i.e., 45% in sensitized individuals is higher compared to non-sensitized individuals.50% of sensitized patients showed well-controlled symptoms and 62.16% showed controlled symptoms in non-sensitized patients. As complete symptom control is the primary aim in the management of asthma when both uncontrolled and partly controlled were made into a single group 50% of sensitized patients showed well-controlled symptoms whereas 62.16% showed well-controlled symptoms in non-sensitized groups.

In the previous study to deduce the clinical significance of Aspergillus sensitization in asthma[16,] it was concluded that there was an only a weak association between Aspergillus sensitization and asthma severity. In our study, statistical significance was not obtained in establishing a causal role in determining the severity of asthma. The most probable reason might be the small sample size. The peculiar results obtained from the study include the proportion of patients with uncontrolled symptoms was more in aspergillus sensitized group. The implication of establishing fungal sensitized asthma is in the therapeutic interventions available anti-fungal therapy showing promising results[23]. Next implication is the theory of continuum of asthma SAFS ABPA with different degrees of fungal hypersensitivity with interventions preventing the progression of disease[10]. Limitations of the study Sample size of 57 were less than was calculated. As patients were required to visit at multiple intervals for investigation of Aspergillus sensitization and ruling out of ABPA, patients were lost to follow up. As our centre is a tertiary care centre, patients who were already treated in primary health care centres were enrolled in this study. This might have lead to modification of allergy tests and disease control rather than in treatment naïve patients. Severe asthma is defined as the disease that requires step 4 or steps 5 treatment [8] but the patient might get stepped up or down based on the patient's control of symptoms whereas GINA symptom control or ACT after at least 1 month of treatment better relates to the severity of the disease. The ambiguity of labelling a disease to be severe asthma still persists, as asthma is a chronic disease even though it can be controlled perfectly by medications. Aspergillus is peculiar funguses as it manifests all different levels of hypersensitivity, but the clinical significance of its sensitisation needs to be evaluated further to prove the causal relation. The antigen used in SPT is a crude antigen with cross-reactivity and there is no specific gold standard test for Aspergillus sensitization and clinical allergy. This was partly alleviated in our study by usage of both specific IgE and SPT for Aspergillus.

The proposed SAFS criteria include: Severe asthma, Aspergillus skin test positive/other fungal skin tests positive, Aspergillus-specific IgE positivity/other fungal-specific IgE positivity

When properly evaluated in further studies may lead to specific therapies. Although preliminary evidence of this study and the previous studies suggest strong evidence of linking asthma severity and fungal sensitization, further clarifications that need to be addressed include: Is fungal colonization adequate for making asthma severe?, Is Body's immune responses/hypersensitivity lead to lung damage causing severe asthma? Are Fungal allergens and proteases that damage epithelium responsible for the severity of asthma?, Regional differences in the environment leading to varying sensitization patterns, thus varying prevalence of SAFS and ABPA.

CONCLUSION

Aspergillus sensitization is a significant step in the natural history of disease which leads to an allergic continuum of diseases with hypersensitivity at one end and bronchial asthma at the other end. The results of the study are as follows: Severity of asthma is associated at least partially to fungal sensitization with sensitisation to Aspergillus at a prime point of pathogenesis. Aspergillus sensitization is significantly associated with bronchiectasis even in the absence of clinical features. Other findings like centrilobular nodules, mosaic perfusion and ground glassing were more common in sensitized individuals. The direct relation between Aspergillus sensitization and spirometry is not proven. Sensitized individuals had uncontrolled symptoms in a higher proportion than non-sensitized individuals but were not significant.

Conflict of interests: There are no conflicts of interest.

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