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Aspergillus Antigen Hypersensitivity - A Severity Marker of Bronchial Asthma? - A Hospital Based Comparative Study

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ABSTRACT

Background: Asthma is an inflammatory disease characterized by airway hyper-responsiveness which is a significant public health problem with more than 300 million affected individuals. About two third of asthmatic patients are atopic to common allergens. Only a few studies specifically evaluated the relation between *Aspergillus* sensitization and severity of bronchial asthma and none from this part of the country.
Methods: This was a hospital based non-interventional observational study of 100 asthmatic patients. After obtaining informed consent and applying necessary inclusion and exclusion criteria, the study population was assessed in detail with set proforma and spirometry before and after bronchodilation. The clinical profile of bronchial asthma and pattern of *Aspergillus* sensitivity in this part of the country was assessed. The association of *Aspergillus* antigen hypersensitivity with severity of bronchial asthma was an integral part of this study.
Results: The mean age of study group was 41.7 years with majority being house wives. Allergy for dust and mites were present in 97%. Cough breathlessness and rhinitis were the major symptoms and polyphonic wheeze the major sign. Prevalence of *Aspergillus* hypersensitivity was 34% and *Aspergillus fumigates* was the most common strain responsible for the same. Spirometry revealed increased severity of bronchial asthma among the sensitive group.
Conclusions: Patients with *Aspergillus* hypersensitivity had significantly worse clinical course, more hospitalizations, more clinical signs and a much worse pulmonary function test. So any patient with bronchial asthma it would be advisable to do an intradermal *Aspergillus* testing to predict the clinical course.

Keywords: *Aspergillus fumigates*, bronchial asthma, hypersensitivity, pulmonary function test, allergy, intradermal antigen testing

INTRODUCTION

Inhalant allergens especially spore forming fungi like *Aspergillus*, play a key role in bringing upon inflammation in the airways. [1] The fungi derive its name from its resemblance to the brush aspergillum, used for sprinkling holy water. The ubiquitous spores inhaled by everyone though seldom have any effect in healthy individuals, are trapped in thick and viscid secretions in asthmatic subjects which on continuous inhalation triggers asthma. The clinical spectrum of *Aspergillus* associated hypersensitivity respiratory disorders include *Aspergillus* induced asthma, allergic bronchopulmonary aspergillosis, allergic *aspergillus* sinusitis. [2] Hypersensitivity pneumonitis may also be caused by *Aspergillus*, but is generally seen in non atopic individuals.

Aspergillus induced asthma is yet to receive the recognition that it deserves. *Aspergillus* sensitization in patients with asthma not only increases the severity of the disease but also is responsible for clinical

entities like allergic bronchopulmonary aspergillosis and allergic *Aspergillus* sinusitis. It is thus crucial to screen all asthmatic subjects for sensitization to *Aspergillus* antigens so as to identify those at risk. Here in this study it was attempted to find out the prevalence of *Aspergillus* hypersensitivity in bronchial asthma patients presenting to a tertiary medical college in Kerala. No study on the topic has been conducted in this part of the state even though prevalence of bronchial asthma is on the rise. By early identification of *Aspergillus* hypersensitivity, necessary precautions and close follow up may be planned to prevent serious complications that they are prone to later. This study benefited those asthmatic patients with undetected *Aspergillus* hypersensitivity by an early diagnosis.

MATERIALS AND METHODS

Objectives of study: The objectives of this study were to study the clinical profile of patients with bronchial asthma presenting to our hospital, know the most prevalent subspecies of *Aspergillus* causing sensitisation in bronchial asthma in our locality and to know the association between *Aspergillus* antigen hypersensitivity and severity of bronchial asthma.

Study area: The study was a hospital based non-interventional observational cross sectional study conducted in MES Medical College Hospital, Perinthalmanna, Malappuram, Kerala.

Study period: Study period was taken as one year

Study population:

Inclusion criteria: All the people more than fifteen years of age presented to MES Medical College during the period of study with at least one of the three below mentioned conditions were included in the study irrespective of sex and locality. The conditions were 1) patients diagnosed to have bronchial asthma, 2) patients with history of recurrent or episodic attacks of chest tightness, breathlessness and cough (especially nocturnal), 3) patients who had wheeze on auscultation of chest.

Exclusion criteria: The people excluded from study were 1) those aged less than 15 years and more than 70 years, 2) those with diagnosis of allergic bronchopulmonary aspergillosis or chronic obstructive pulmonary disease, 3) pregnant women, 4) those with immunosuppressive conditions such as chronic liver disease, renal failure, uncontrolled diabetes mellitus, chronic heart failure, immunosuppressive drugs other than glucocorticoids for controlling asthma and 5) those not willing to give informed consent.

Sample size: After applying the above inclusion and exclusion criteria 100 patients were included in the study.

Data collection technique and tools: After getting informed consent meticulous clinical history of all patients were taken. It included present symptoms, allergy to dust, smoke or smell, history of atopy, eczema or food allergy and number of hospitalization in a year. Co-morbidities were enquired of along with relevant personal history. Thorough general and respiratory system examination were done and positive findings were noted. Assessment of severity of asthma was carried according to the 2002 Global Initiative for Asthma (GINA) recommendations (given below in table 1), which include the effect of treatment on disease severity.

Table 1: GINA Recommendations

Characteristic	Controlled asthma (all characteristic to be present)	Partially controlled asthma (any characteristic present in any week)	Uncontrolled asthma
Day time symptoms	Twice or less/week	>Twice/week	Three or more characteristics present in any week
Limitation to activities	None	Any	
Nocturnal symptoms	None	Any	
Need for rescuer medicine	Twice or less/week	>Twice/week	
Lung function (FEV_1 or PEF)	Normal	<80% of predicted or best personal (if known)	

Spirometric indices such as forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio and Peak Expiratory Flow

Rate (PEFR) were measured before and after administration of 400µg of inhaled salbutamol using the American Thoracic Society guidelines. [3] The highest measurements from among the three technically acceptable and reproducible manoeuvres were expressed. The spirometer was frequently calibrated to ensure performance. Bronchodilator reversibility was considered significant if, after inhalation of 400µg of salbutamol, the FEV_1 and/or FVC increased by ≥12%.

The *Aspergillus* skin test was done with pre-formed antigens of *A.fumigatus*, *A.niger*, *A.flavus* and *A.terreus*. Commercially available antigens were used in the study. The available antigens were made in the following way. (a) The specific antigen of *Aspergillus* species obtained from stock culture was incubated at 25°C in two Sabouraud's dextrose agar slants; (b) after obtaining typical growth upon incubation, the organism was inoculated in the glucose asparagine broth and incubated at 25 - 30°C for 3–4 weeks. The culture was then treated with merthiolate and then checked for microbial contamination; (c) the broth culture was then filtered using Seitz filter and then sterilised using millipore filters; (d) the precipitate was dissolved in distilled water and dialysed against distilled water. The dialysate was then freeze dried after ensuring that it is endotoxin (limulus amoebocyte lysate assay) and bacteria (blood agar, brain heart infusion broth and thioglycollate broth) free; (v) the total protein content was assessed by the Lowry method and the final concentration of the protein was standardised to 100 PNU/ml (1 PNU = 0.00001 mg/ml). The intradermal skin test was performed as follows: (a) the skin test was performed by injecting 0.2 ml of the *Aspergillus* antigen (100 PNU/ml) intradermally in the forearm. For negative control, 0.2 ml of phosphate buffered saline was injected intradermally in the other forearm. No positive control was used; (ii) the injection site was examined every 15 min for 1 h. *Aspergillus* sensitisation was defined if a wheal and erythema developed within 1 min, reached a maximum after 10–20 min and resolved within 1 h; with the antigen arm skin reaction diameter being at least 8 mm more than that on the control arm.

Statistical analysis: The collected data was entered in Microsoft Office Excel 2007 and was analysed with appropriate statistical software (Epi-info v3.4.3). Tests used in the process were independent t test and chi square test and a p value <0.05 was taken as significant.

RESULTS

A total of hundred patients were included in this study. Mean age of the study population was 41.7 years and there were 48 house wives, 25 manual laborers and 27 skilled professionals. As the total count of my study population was 100, number of patients with each of the below variable is equal as percentage of the same in study population. 90 out of 100 patients were having cough, 83 had breathlessness, 74 had rhinitis, and 25 had fever. Limitation of daily routine activities was noted in 17 and marked nocturnal symptoms were seen in 40. Day time symptoms were present for less than twice a week in 62 patients and need for rescuer medications for more than twice a week was present for 67. Past history of atopy was present in 31. Allergy to smoke or dust or both was seen in 97 out of 100 patients. There were no hospitalizations for 74 in the past and 18 were hospitalized for one to three times in last year while remaining eight had more than three hospitalizations during same period. Mean pulse rate was 85.1/minute with a maximum pulse rate 104 beats per minute and minimum 68 beats per minute. Mean blood pressure of my study population was 128/78 mm of Hg. Mean respiratory rate was 20. Only 3 patients were febrile at the time of examination. Most common examination sign was polyphonic wheeze. Mean Forced expiratory volume for 1st second (FEV_1) of the study group before giving nebulisation with bronchodilator was 66.2 ± 14.8%.

After nebulisation the mean FEV_1 was 78.1 ± 10.4%. The mean Forced vital capacity (FVC) values before and after nebulisation were 68.4 ± 12.3% and 79.1 ± 9.3% respectively. Mean FEV_1/FVC was 88.1 ± 9.2. Mean peak expiratory flow rate (PEFR) values of the study group before and after nebulisation were 68 ± 11.7 and 79.4 ± 11.2 respectively.

Intradermal test was done for all 100 patients with four different strains of *Aspergillus* antigens namely *A.fumigatus*, *A.niger, A.flavus* and *A.terreus*. Out of 100, 34 patients were found to be positive for *Aspergillus* skin test for atleast one strain. Many were hypersensitive to more than one strain and a few, to all four strains. The strain to which most patients were hypersensitive was *A.fumigatus*. 27 out of 34 patients were hypersensitive to the same which accounted to 79.4%. It was followed by *A.niger* which was hypersensitive to 21 patients (61.8%). 19 patients were hypersensitive to *A.flavus* (55.9%) and 41.2% (14 patients) were hypersensitive to *A.terreus*.

Moving on to the most important aspect of study, how *aspergillus* hypersensitivity affected the severity of bronchial asthma. Here we compared changes in different aspects of clinical significance between the 34 patients who were hypersensitive to *Aspergillus* antigen and the 66 who were not. The severity of asthma was assessed by GINA guidelines mentioned previously. Day time symptoms (DTS) were significantly higher among the hypersensitive group, and so were loss of activity (LOA), Nocturnal symptoms (NS) and need for rescuer medications. There was a statistically significant difference between the two groups highlighted in table 2 below.

Table 2: Frequency of severity of asthma among hypersensitive group and others

Symptoms		Skin test negative		Skin test positive		χ^2	P
		Count	Percent	Count	Percent		
Day Time Symptoms	<Twice a week	54	81.8	8	23.5	32.36**	0.001
	>Twice a week	12	18.2	26	76.5		
Loss Of Activity	Absent	63	95.5	20	58.8	21.34**	0.001
	Present	3	4.5	14	41.2		
Nocturnal Symptoms	Absent	52	78.8	8	23.5	28.55**	0.001
	Present	14	21.2	26	76.5		
Need for Rescuer Medications	<Twice a week	58	87.9	9	26.5	38.27**	0.001
	>Twice a week	8	12.1	25	73.5		

**Statistically significant at 0.01 levels

There was no significance for past history of allergy to dust, smoke and smell as well as for atopy, eczema and food allergies. However past history of hospitalizations was significantly higher among the hypersensitive group. There was no hospitalization for 84.8% of patients who were not hypersensitive for *Aspergillus*; where as 23.5% of aspergillus hypersensitive patients were hospitalized for more than four times over the last year which was statistically significant. Seasonal variation of symptoms was more with hypersensitive group. The details are given below in table 3.

Table 3: History and *Aspergillus* hypersensitivity

Past history		Skin test negative		Skin test positive		χ^2	P
		Count	Percent	Count	Percent		
Past h/o allergy	None	3	4.5	0	0.0	1.59	0.207
	Allergy to dust, smoke, smell	63	95.5	34	100.0		
Past h/o atopy	Absent	46	69.7	23	67.6	0.04	0.834
	Present	20	30.3	11	32.4		
Past h/o eczema	Absent	62	93.9	31	91.2	0.26	0.608
	Present	4	6.1	3	8.8		
Past h/o food allergy	Absent	59	89.4	29	85.3	0.36	0.550
	Present	7	10.6	5	14.7		
Number of hospitalizations	Nil	56	84.8	18	52.9	19.49**	0.001
	1 – 3	10	15.2	8	23.5		
	4 – 8	0	0.0	8	23.5		
Seasonal Variation	Absent	15	22.7	2	5.9	4.51*	0.034
	Present	51	77.3	32	94.1		

** Statistically significant at 0.01 level *Significant at 0.05 level

Significant auscultatory findings were present in 92.2% of patients with *Aspergillus* hypersensitivity where as among those without hypersensitivity less than half had clinical signs which was again statistically significant and given in table 4 below.

Table 4: Clinical signs and Aspergillus hypersensitivity

Clinical examination		Skin test negative		Skin test positive		χ^2	P
		Count	Percent	Count	Percent		
Respi signs	Absent	38	57.6	3	8.8	22.05**	0.001
	Present	28	42.4	31	91.2		

** Significant at 0.01 levels

Coming to the spirometry; mean values of Forced Expiratory Volume in 1st second (FEV_1), Forced Vital Capacity (FVC), FEV_1 / FVC and Peak Expiratory Flow Rate (PEFR) were calculated separately for those 34 patients hypersensitive to *Aspergillus* antigen and those 66 who were not. Mean values were assessed using independent t test and t values of more than 2.54 were taken as statistically significant and p values of the same were calculated for added significance. The results are summarised in table 5 below.

Table 5: Spirometry and *Aspergillus* hypersensitivity

Forced Expiratory Volume in 1st second (FEV_1)						
	Skin Test	Mean	SD	N	T	P
Pre bronchodilator	Negative	74.0	6.1	66	10.9**	0.001
	Positive	51.0	15.0	34		
Post bronchodilator	Negative	82.8	6.0	66	8.08**	0.001
	Positive	69.0	11.1	34		
Forced Vital Capacity (FVC)						
	Skin Test	Mean	SD	N	T	P
Pre bronchodilator	Negative	74.7	5.7	66	10.22**	0.001
	Positive	56.1	12.6	34		
Post bronchodilator	Negative	83.1	5.8	66	7.42**	0.001
	Positive	71.4	10.0	34		
FEV_1 / FVC						
Skin Test		Mean	SD	N	T	P
Negative		90.8	6.4	66	4.5**	0.001
Positive		82.9	11.4	34		
Peak Expiratory Flow Rate (PEFR)						
	Skin Test	Mean	SD	N	T	P
Pre bronchodilator	Negative	74.2	5.8	66	10.94**	0.001
	Positive	56.0	10.9	34		
Post bronchodilator	Negative	84.7	5.0	66	8.91**	0.001
	Positive	69.1	12.5	34		

**Statistically significant at 0.01 levels

From the table it was clear all the FEV_1, FVC, FEV_1/FVC and PEFR mean values were significantly lower in *Aspergillus* hypersensitive group when compared to those not sensitive and it remained lower even after bronchodilator administration. Even the hallmark of bronchial asthma, reversibility of inflammation with bronchodilators, was less in those patients hypersensitive to *Aspergillus*.

DISCUSSION

Mean age group of the study population was found out as 41.7 ± 13.4 years. Most of the studies showed a male predominance pattern. The difference here may be due to exposure to dust and smoke from traditional type of kitchens as most of the female population in my study were housewives and a significant number are allergic to dust and smoke. In a multicentre study conducted in India by Dr. S.K. Jindal *et al* sponsored by Indian Council of Medical Research, it had been found out that females outnumbered males with a male female ratio of 0.63 in South India and almost 70% women of study population were housewives. [4] This finding was also brought out by a study in Spain in 2013 by Martínez-Moragón E *et al* where mean age

of study population was 50 years, 64.6% were women and majority were house wives and unemployed. [5] Cough was the predominant symptom in all the above studies. Past history of atopy was noted in 31%. 20% of study population had atopy in a similar study in Vishakapattanam. [6] Allergy to dust, smoke or both were noticed in 97% of my study population which is the highest in any study to date. The pulmonary function tests were done before and after bronchodilation in all the hundred patients. The mean values were furnished above in results. There was significant reversibility noticed among the pre and post bronchodilation spirometries. Most significant reduction in mean was noted in Forced Expiratory Volume for 1st second, followed by peak expiratory flow rate. Pulmonary function tests worsened over increasing age as well. The values were very much identical to the one found out by Madan *et al* in Punjab. [7] Pascual *et al* reported that clinically, airflow obstruction in asthma often is not fully reversible, and many asthmatic subjects experience an accelerated and progressive loss of lung function over time. [8] Lange *et al* proved that adults with asthma have substantially greater declines in forced expiratory volume in 1s (FEV1) over time in comparison with healthy subjects. [9]

Prevalence of *Aspergillus* antigen hypersensitivity in this study population was noted as 34%. *Aspergillus fumigates* hypersensitivity was seen among 27 out of 34 hypersensitive patients (79.4%) closely followed by *A.niger* (61.8%), *A.flavus* (55.9%) and *A.terreus* (41.2%). Many were hypersensitive to multiple *aspergillus* antigen and a few were hypersensitive to all four tested. The reported frequency of *aspergillus* sensitivity in patients with asthma had varied from 16-38% in different parts of world and in a study from Delhi 30 out of 105 patients with asthma revealed to have hypersensitivity to *aspergillus* antigen. [10] The investigators also recorded that a positive *Aspergillus* skin test was related to severity of airway obstruction such that asthma was more severe in patients hypersensitive to *Aspergillus* than to other allergens. A European committee respiratory health survey in 30 centres demonstrated that the frequency of sensitization to *Alternaria alternata* and *Cladosporium herbarum* increased significantly with increasing asthma severity. [11] Previous studies have shown that sensitization or exposure to fungi increases the risk of death from asthma and also acute attacks of asthma requiring intensive care unit admissions. [12,13]

In this study day time symptoms, nocturnal symptoms, loss of activities and need for rescuer medications were significantly higher in patients with *Aspergillus* antigen hypersensitivity. Generally severity of asthma was more among patients with *Aspergillus* antigen hypersensitivity. 76.5% of hypersensitive group had experienced day time symptoms more than twice/week. 76.5% had nocturnal symptoms and 73.5% needed rescuer medications for more than twice a week. There are no much Indian studies and none from this area of country to compare these findings. Seasonal variation was also found significantly higher among my study population with *Aspergillus* antigen hypersensitivity which was again, a unique finding. Respiratory signs were significantly more among the group who were hypersensitive to *Aspergillus* antigen. Polyphonic wheeze was heard in 91.2% of the patients who were hypersensitive to *aspergillus* where as majority of patients (57.6%) who were not hypersensitive had normal breath sounds with no added sounds. Worsening of asthma clinically with *Aspergillus* antigen hypersensitivity had been brought to notice prior by Ownby DR *et al*. [14] Pulmonary function test was also done in all patients. Mean forced expiratory volume in 1st second before bronchodilator administration was 54% in hypersensitive group compared to 74% in non hypersensitive group. After administration of bronchodilator, means improved to 69% in hypersensitive group and 82.8% in non

hypersensitive groups. The differences in means were statistically significant and there was a significant reduction in forced expiratory volume in 1st second among those patients hypersensitive to *Aspergillus* antigen. Similarly mean forced vital capacity was 56.1% before bronchodilator administration and 71.4% after bronchodilator administration among hypersensitive group compared to 74.7% and 83.1% among non hypersensitive group respectively. Again mean forced vital capacities before and after bronchodilator administration were significantly low among those hypersensitive to *Aspergillus* antigen. The same applied to mean FEV_1/FVC. It was significantly low among those hypersensitive to *Aspergillus* antigen (82.9) compared to those not hypersensitive (90.8). Mean Peak Expiratory Flow Rates before and after bronchodilator administration among those not hypersensitive to *Aspergillus* antigen were 74.2 and 84.7 respectively. That was also significantly low in those hypersensitive to *Aspergillus* antigen, the values being 56 and 69.1 respectively. So pulmonary function test showed more detrimental pattern in those hypersensitive to *Aspergillus* antigen than the rest who were not. Similar patterns were obtained in studies conducted by Nichols *et al*. [15]

CONCLUSION

Clinical profile of bronchial asthma in this part of country is not significantly different from other parts. Mean age group and majority age groups are comparable. Slight female predominance was noted with majority house wives. Cough, breathlessness and rhinitis were common symptoms in this part of country with nearly half experiencing nocturnal symptoms. One third of my study population gave past history of atopy. Majority of the study population gave history of allergy to dust, smoke or both. Three fourth of my study population had no hospitalizations in last year. However on examination, more than half had polyphonic wheeze on auscultation. Pulmonary function test was also showing reduction in Forced Expiratory Volume after 1st second, Forced Vital Capacity, FEV_1/FVC and Peak Expiratory Flow Rate and they were reversible to some extend by bronchodilator nebulisation.

Prevalence of *Aspergillus* antigen hypersensitivity was noted as 34%. Most common strain responsible was *A.fumigatus*, closely followed by *A.niger* and *A.flavus*. Those who were hypersensitive to *Aspergillus* antigen were having a significantly worse clinical profile with more frequency of day time symptoms, nocturnal symptoms, need for medications. There was more number of hospitalizations, higher frequency of exposure to moulds and more seasonal variation. Auscultatory findings were far more among those with *Aspergillus* antigen hypersensitivity. Pulmonary function test was more compromised in patients who were hypersensitive to *Aspergillus* antigen with significantly low forced expiratory volume after 1st second, forced vital capacity and peak expiratory flow rate. Reversibility after bronchodilator administration was also minimal among those with *Aspergillus* antigen hypersensitivity. So any patient coming with bronchial asthma it is always better to do a skin testing for *Aspergillus* antigen hypersensitivity. It will be wise to closely follow up those with *Aspergillus* hypersensitivity as they are more prone for poor outcome and more complications.

Limitations:

Blood investigations suggesting allergic responses like serum IgE and absolute eosinophil count assessment were not done in this study due to financial constraints. No radiological assessment was done as it was outside scope of the study and would cause unnecessary radiation exposure to patients. Other aspects of *Aspergillus* hypersensitivity like allergic sinusitis, allergic bronchopulmonary aspergillosis were not studied as they were out of scope of this study.

Recommendations:

All patients with bronchial asthma must undergo a skin testing for hypersensitivity with

Aspergillus antigen. Those hypersensitive to *Aspergillus* antigen must be followed up regularly. Life style modifications should be given to those housewives allergic to smoke and those manual labourers allergic to dust as to prevent further exacerbations. Large prospective community based studies may be conducted to know the clinical profile of bronchial asthma and its association with *Aspergillus* hypersensitivity in this area of country as asthma is on the rise here. Studies may be conducted with financial grant as most of required blood investigations are costly. Tests with more sensitivity, specificity and positive predictive value shall be devised for detecting *Aspergillus* hypersensitivity as it is one factor that will completely change the course of disease.

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