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Study to Find Clinical Characteristics of ABPA in Patients of Severe Bronchial Asthma and Its Relation with Serum Ige Level at Teriary Care Center North India

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Abstract

Introduction: Allergic bronchopulmonary aspergillosis (ABPA) is an idiopathic inflammatory disease of the lung, characterized by an allergic inflammatory response to colonization of the airways by Aspergillus fumigatus or other fungi. Untreated or inadequatetreatment may lead to poor outcome in patients. Raised level of serum IgE of more than 1000 IU/ML have been considered as one if theimportant diagnostic criteria for ABPA, however relation of serum IgE withs severity ofdiseases is lacking. This study was conducted to find out level of serum IgE in patients ofABPA and to find out corelation of Serum IgE with duration of symptoms and diseasesseverity.

Material and Method: This was prospective, single centre observational at tertiary carecentre.A completeclinical history and examination, and routine investigations, chest X-ray PAview, sputum for AFB was done. Spirometry was done to assess severity of obstructionpresent in patients. Total serum Immunoglobulin-E, aspergillus specific serum IgE and IgG. and absolute serum eosinophilia was done in all patients. Data was analysed using SPSS22.0. software using percentage and persons Chi squire test. and ANOVA test.

Results: 45 patients were selected for the study after screening of 250 patients of bronchialasthma. Mean age was 29.18 yrs with majority of male. Mean duration of illness was9.6±6.4.yrs.31% patients were prescribed ATT without confirmatory evidence Mean serumIgE was 2509 IU/ml mean serum IgE was higher in female patients as compared to male.There was no significant corelation between absolute serum eosinophil count and serum IgElevel, However there was significant inverse corelation between mean serum IgE and severityof obstruction on spirometry

Discussion: Prevalence of ABPA was 18%.Although child of age 8 yrs was found sufferingfrom ABPA, There was wide variability in clinical presentation and mean serum IgE leveland there was no significant association between serum IgE with clinical presentation orduration of illness but it was was found that higher Serum IgE level was associated with poorventilatory

function.

Conclusion: ABPA has wide variability in its clinical presentation and is difficult to diagnosein cases of severe persistent bronchial asthma, A high index of suspicion and throughinvestigation may help to identify and treat these patients early.

Introduction

Aspergillus is a saprophytic fungus found ubiquios in soil ,air and organic decaying matter present indoor as well as outdoor. Multiple species of aspergillus is been identified. Although aspergillus is not pathogenicbut favourable environmentcan lead invasion of the human tissue and may present as diverse manifestation. Among all the species Aspergillus fumigatus (A. fumigatus) is most common to infect humans. It can affect any organ of the body but respiratory system is most vulnerable to get infection first and most. Aspergillus can affect lung in both non invasive and invasive form.Non invasive form of infectionmay include saprophytic colonization (Aspergilloma)or allergic hypersensitivity reaction while invasive forms include invasive pulmonary aspergillosis,-Tracheobronchial aspergillosis and chronic necrotizing pulmonary aspergillosis.

Allergic bronchopulmonary aspergillosis (ABPA) is an idiopathic inflammatory disease of the lung, characterized by an allergic inflammatory response to colonization of the airways by Aspergillus fumigatus or other fungi.

The precise prevalence of ABPA is unknown, in part due to variability in diagnostic criteria used in various studies, the lack of distinction between ABPA and mould sensitive asthma, and delays in the diagnosis of patients with long-standing disease; however, it is clear that ABPA is a relatively common entity. Estimates are that true ABPA complicates approximately 7% to 14% of cases of chronic steroid–dependent asthma and approximately 7% to 15% of cases of cystic fibrosis [15,16]

Although ABPA typically presents in patients with a history of difficult-to-control asthma, the spectrum of presentation is highly variable and should be considered in any patient with severe asthma and hypersensitivity to A. fumigatus . Raised level of serum IgE have been considered as one if the important diagnostic criteria for ABPA In all the recommendation. A cut of value of more than 1000 IU/ml has been considered as diagnostic along with anothercriteria [8]. However relation of serum IgE with duration of symptoms or other parameter has ot been established .This study was conducted to find out level of serum IgE in patients who were diagnosed as ABPA and to find out corelation of Serum IgE with duration of symptoms and diseases severity

Material and Methods

This prospective, single centre observationalstudy was conducted in the Department of Tuberculosis and Respiratory Diseases,G.S.V.M.Medical College, Kanpur from over 12 months

Patients ofany age and of either sex attending hospital with history of moderate to severe asthmawere evaluated for diagnosis and characteristics of various parameters of allergic bronchopulmonary aspergillosis consecutively. An informed consent was taken from all the patients.Those who were not willing or are unable to travel for investigation frequently were removed from the study. Patients who lost to follow up during investigations were also removed from the analysis.Criteria proposed by rosenenberg and patterson. (1977) for the diagnosis of ABPA was used.

A complete clinical history and examination, as per standard practice were done in these patients. History was also focussed on area of living whether rural or urban and possibility of exposure to hot and humid condition. Patients were also asked about history of asthma or similar illness in family.All patientswere subjected to routine investigations such as , complete blood count, absolute eosinophil count, KFT, LFT, serum electrolytes and chest X-ray PA view, sputum for AFB , sputum for fungal staining and bacterial culture sensitivity

Spirometry was done to establish the diagnosis of bronchial asthma and severity of obstruction present in patients. They were also subjected to total serum Immunoglobulin-E,aspergillus specific serum IgE and IgG.

HRCT thorax was also done in patients to find out presence or absence, of bronchiectasis, to assess other radiological feature and severity of the involvement of the lung.No genetic testing or congenital anomelies related test could be performed in patiens of young age or in patients having similar history in family

Datawas analysed using SPSS22.0.Catogerical variable were analysed using percentage and persons Chi squire test. Quantitive variables were analysed using mean and slandered deviation and ANOVA. p value of less than0.05 was considered significant.

Observation

Over the study period 45 patients were selected for the study after screening of 250 patients of bronchial asthma. Therewere almost equal no. of male and female patients in the study. Patients were having lowest age of 8 years and highest age of 55 yearswith Mean age of the study population was 29.18±11.9. Mean age of male population was 28.18±13.39 whileof female population was 30.18±10.42. In this study, maximum no of patients were in age group 21-30 years.

Maximum patients of the study population were from rural area (62.2%) with equal ratio of male and female.

Duration of symptoms varied ranging from 5 yr to 20 years with Mean duration of illness was 9.6±6.4. Only around 24.4%had duration of symptoms equal or less than 5 years,probably suggesting that duration of asthma is somehow related with presence of ABPA

Breathlessness was the most common symptom, being present in all patients. This was followed by cough in 84%, wheezing 62%, expectoration in 55% and chest tightness in 44.5%. Haemoptysis was present in 20% of patients.

X ray was done in all patients ofour study , 24(53.3%) chest x-ray had infiltration, followed by bronchiectasis in 12(26.7%) , 5(11.1%)had infiltration plus bronchiectasis. chest x-ray was normal in 4 (8.9%) patients. Since we could not do serial Xray we could not find fleeting opacity or progression or regression of the lesion.

CT thorax was done inonly 24 patientsand out of them 70% had central bronchiectasis out of which 12 patients have isolated bronchiectasis while 5 patients have bronchiectasis with infiltrative shadow[9]. No migrating shadow could be found in the CT .Because of paucity of the data no correlation could be drawn from the finding. However there was only one patient who had normal CT thorax finding in spite of having sign and symptoms strongly correlating with ABPA. we could not find fleeting shadow in any of the patient who have CT done more than once. Interestingly 16% patients have hyperinflation and bullae present in their CT Findings

14 patients out of 45 patients(31.1%) had been prescribed anti-tubercular(ATT) drugs during their illness for significant duration without any improvement in symptomatology. All patients were prescribed ATT on basis of X Ray and symptoms and none were microbiologically confirmed.

Total serum immunoglobulin IgE was measured in all the patients. .SerumIgE was found to be very high in all the patients with mean serum IgE level of 2509 IU /Ml. It was found that female patients have higher serum IgE value as compared to male patients.(Table -1) how ever there were 20 % patients having serum IgE more than 4000IU/ml. Maximum no. of patients(42.2%) in our study cohort, had serum Ig-E more than 3000 IU/ml. The mean duration of symptoms wasnot much different in different IgE groups. We tried to find out any correlation of total serum IgE level with age and sex distribution but there could not be ,as there were equal distribution of the patient with various Serum IgE level in all age group.

However whenwe observed mean serum IgE of maximum no. of patients (age group 21-40 years comprising of around 67%) it comes to be Ig-E Level 2335±914. Patients in age group below/equal to 10 years and 41-50 yearshad mean Ig-E 4025±3436 and 2927±1030 respectively. In the age group of 0-10 yrs mean serum IgE was higher because of one patients having value of more than 9000 IU leading to high mean value. Other age groups have only 2 or 3 patients that's why mean serum IgE value can not be interpreted

Serum Total Ig-E(IU/ml)	Male	Female	Total
>3000	9	10	19
2000-3000	5	7	12
1000-2000	8	6	14
TOTAL	22	23	45
MEAN	2227±918	2779±1824	2509±1464

Table 1: Total serum IgE and sex distribution of the patients

Serum eosinophilia was measuredin all these patients and tried to find out correlation between raised serum eosinophil count and serum IgE level .Peripheral eosinophilia was found to be raised in all the patients but there was no correlation between raised serum IgE and peripheral eosinophilia. patients having very high serum IgE were found to have mild peripheral eosinophilia.

Absolute eosinophilia	Total Serum Ig E			Mean S.IgE Level	Total
	1000-2000	2000-3000	>3000		
<500	8	5	4	2575±21	16(35.6%)
500-1000	5	5	8	2503±82	18(40%%)
>1000	1	2	7	2415±10	11(24.4%)
TOTAL	14	12	19	2509±14	45 (100%)
Mean Eosinophilia	459±344.6	533±266.4	946±502		

Table 2: Corelation of absolute eosinophilia and serum IgE level in patients of ABPA

Chi squire test -o,123

ANNOVA TEST0.002

Above table show that there was no significant corelation between absolute eosinophilia and serum IgE but there was significant correlation with mean serum eosinophilia andserum IgE level in patients

Spirometry finding were assessed in all the patients Maximum patients 35 (78%). have features of obstructive lung diseases with good reversibility 6 (13.4)% of the patients have restrictive pattern on spirometric examination while 4 patients(8.9%)have normal spirometric findings. Out of 35 patients having obstructive pattern, obstruction was moderate in 18 patient(40%)followed by mildin 10 patients(22.2%) and severe obstruction in 7 patients(15.5%). There was no significant corelation between severity of obstruction in spirometric finding and serum IgE level of the patients.

Mean FEV1 of the study group was 70.40 ±19.2. Patients with total serum Ig-E between 1000-2000 , mean FEV1 was 86.07±10.8, it was 74.25±14.46 in group with total serum Ig-E between 2000-3000 and it was 56.42±16.95 in group with total serum Ig-E more than 3000.

Spirometric finding	Total Serum Ig E			
	1000-2000	2000-3000	>3000	Total
Normal	3	1	0	4(8.9%)
Restrictive	1	2	3	6(13.4%)
Mild Obstruction	6	3	1	10(22.2%)
Moderate Obstruction	4	6	8	18(40%)
Severe Obstruction	0	0	7	7(15.5%)
MeanFEV1(% FVC)	86.07±10.8	74.25±14.46	56.42±16.95	70.40±19.25

Table 3: Spirometry Finding and its corelation with serum IgE

Chi squire test value-0.103

ANNOVA =0,001

Chai squire test was applied to find out corelation of different spirometirc finding with serum eosinophilia and it was found not significant, while ANNOVA was applied to find corelation between mean FEV1 Value with serum IgE and its was found that there is significant inverse corelation between mean FEV1 and serum IgE Value.

Discussion

This hospital based observationalstudy was conducted oncharacteristics of allergic broncho-pulmonary aspergillosis in clinical and radiological suspects, Respiratory medicine department of GSVM medical college Kanpur.

We observed that prevalence of ABPA 18% in our study. This observation is higher as compared to previous studies [11].There is possibility of selection biasas this is not population based study and was done at tertiary care centre and we focussed on patients having severe asthma only.

Any age of patients can develop ABPA although mean age was 29 yrs in our study which is less as compared to previous done studies in India [2,4] suggesting that patients of most productive group of society are mostly suffering from the diseases. If we take into the account mean duration of illness of our study which is around 10 years which was similarto other studies from India [4,10,17] this may imply that patients who develop early childhood asthma are prone to develop ABPA as compared to patients with adult onset asthma. Another factor which may lead to development of ABPA in such patients is inadequate treatment of bronchial asthma as most of the patients had history of irregular medication for their asthma. It is likely that ABPA starts early in life and continues, unrecognized, until adulthood. Interestingly, familial cases have been reported, from India and other centers, suggesting that genetic factors underlie development of ABPA. Most common genetic association is with CFTR genes but other association has also been found in smaller studies.

It is difficult to suspect ABPA in patients of severe bronchial asthma. There was no difference in clinical presentation of the patients and all the patients presented with dyspnoea and grade of dyspnoea was disproptionate to the examination finding and cough was also productive . differentiating it from asthma which is predominantly have dry cough.

A significant no of patients(31.1%) had been prescribed anti-tubercular(ATT) drugs during their illness, without any microbiological confirmation which is common among practioners. This lead to poor control of, as well as chances of development of adverse effect of the drug. No confirmatory diagnostic investigation could be found in these patients. These finding are similar to the previous studies [4, 7]. Antitubercular treatment in all our cases were given on the basis of chest X-ray and in most of the cases patients stopped ATT on his own because of no response.

All patients of ABPA had much higher serum IgE ,much above the cut off value for the diagnosis of ABPA. Few patients have value as high as high as more than 5000.

Higher value of serum IgE may indicate either severity or higher immunogenicityof the diseases in our patients.[5, 7]

Corelation with severity of symptoms and duration of illness could not be established in our study as there was no statistical difference in serum IgE Value and duration of illness.

We have serum eosinophil count non significantly distributed among the group although mean serum eosinophiliawas highandis comparable to previous studies. Sputum eosinophilia has not been assessed because of lack of facilitiesin our study although it has shown correlation with severity of asthma.[16, 17]

A consistentcorrelation between serum absolute eosinophilia and serum IgE was not found in subgroup analysisalthoughIt was found that higher serum IgE have higher serum eosinophilia. A larger study with further analysis of inflammatory markers of serum eosinophilia might help us in solving the puzzle of serum eosinophilia and serum IgE corelation

There was inverse correlation between mean serum IgE and severity of obstruction in spirometirc findingand this was similarto the study done by Roshan M Kumar et al(2017)al in case of asthma (17)

Wide variability in presentation and demographic profile of ABPA patients leads to the assumption that there may be a genetic susceptibility in all these patients .It has been observed that in spite of ongoing inflammatory reaction few patients develop bronchiectasis and severe symptoms.

Conclusion

ABPA is complex diseases and is predominantlydisease of adulthood with severe asthma in Indian population. Etiology and precipitating factors may be variable. There was no consistency between serum IgEand severity of symptoms neither with serum eosinophilia. Spirometric finding have inverse correlation with serum eosinophilia.

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