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Clinical-serological clues to *Aspergillus* sensitization in chronic obstructive pulmonary disease

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Abstract:

Chronic obstructive pulmonary disease (COPD) accounts for 35%-55% of the groups manifesting *Aspergillus* sensitization and is considered to be highly associated with severe symptoms. Therefore, it is of interest to evaluate the prevalence of *Aspergillus* sensitization in (COPD) and correlate with seasonal variation and respiratory symptoms. Total IgE and *Aspergillus* specific IgE were measured using ELISA with follow-up of patients during seasonal change. *Aspergillus* sensitization was found in one-third of the patients with COPD with fungal hyphae in sputum samples in 33% samples at enrolment and 40% samples at follow-up. This phenomenon should be considered in COPD patients, especially during exacerbations or emergency admissions.

Keywords: Chronic obstructive pulmonary disease (COPD), *Aspergillus* sensitization, total IgE, *Aspergillus* specific IgE

Background:

The fungus *Aspergillus spp.* is ubiquitous in nature that enters the human body primarily through respiratory tract in the form of spores. *Aspergillus spp.* is known to cause invasive pulmonary disease in immunocompromised individuals. Patients with asthma, bronchiectasis and chronic obstructive pulmonary disease (COPD) are more susceptible to infection by *Aspergillus spp.* This is ascribed to the immunosuppression due to excessive use of antibiotics and glucocorticoids [1]. It has been showed that patients of asthma, bronchiectasis and cystic fibrosis with *Aspergillus* sensitization had poorer clinical outcomes [2-4]. *Aspergillus* sensitization has also been found to occur in patients with COPD [5]. There have been conflicting reports of the clinical impact of *Aspergillus* sensitization in COPD patients [6, 7]. Some authors have reported that *Aspergillus* sensitization in COPD was associated with increased severity of symptoms and frequent clinical exacerbations [6]. Other studies showed a lack of association between *Aspergillus* sensitization with COPD exacerbations and poorer lung function [7]. *Aspergillus* sensitization can be detected by serum levels of *Aspergillus*-specific IgE [8]. Therefore, it is of interest to evaluate the prevalence of *Aspergillus* sensitization in COPD patients and correlate with respiratory symptoms.

Materials and Methods:

This was a cross-sectional study conducted at a rural health research unit and a tertiary level medical college and hospital conducted over a period of two years. Enrolment of patients was done over a period of four months (March – June 2022).

Inclusion criteria:

Patients aged more than 40 years with clinical features suggestive of stable COPD at the time of enrolment (chronic cough, expectoration and/or wheeze for at least three months in the preceding year) visiting the community health center or the Medicine department of the medical college were included in the study.

Exclusion criteria:

Patients having received systemic steroid therapy in the preceding 4 weeks and those with co-morbid conditions such as active pulmonary tuberculosis, interstitial lung disease or severe heart failure were excluded from the study.

Study procedures:

After taking informed consent, demographic details of patients were recorded and a thorough clinical examination performed for grading of the COPD. Pulmonary function tests (PFT) were done and venous blood samples collected for IgE testing. Sputum samples were also collected, wherever possible, for microscopic examination. The enrolled patients were kept under follow-up and re-visit planned between December 2022 to February 2023 at six months after enrolment or a clinical exacerbation, whichever was earlier. At the follow-up visit, clinical examination, PFT and venous blood samples for IgE testing were repeated. The venous blood samples were tested for total IgE and *Aspergillus*-specific IgE by enzyme-linked immunosorbent assay (ELISA). Serum levels of <0.35 IU/ml were considered as normal for *Aspergillus*-specific IgE while levels >0.70 IU/ml were taken as positive, suggesting an allergic response. The serum total and *Aspergillus*-specific IgE levels at the two time points were compared and correlated with clinical features and outcome at the last follow-up visit. The study was approved by the Institutional Ethics Committee of the medical college.

Statistical analysis:

No significant difference was noted in the proportion of cases with total IgE or *Aspergillus*-specific IgE positivity on initial or follow-up visit. There was no significant gender difference in the total IgE or *Aspergillus*-specific IgE positivity. COPD patients with elevated serum *Aspergillus*-specific IgE levels reported more frequent clinical exacerbations and hospitalizations ($P<0.001$) compared to those with normal levels.

Table 1: Clinic-serological parameters of included COPD patients at enrolment and follow-up visit

Parameter	First visit	Follow-up	P value
Serum Total IgE-positive	52 (64.2%)	52 (64.2%)	<0.001
- <200 IU/ml	29	29	

- 200-400 IU/ml	42	18	
- >400 IU/ml	10	34	
<i>Aspergillus</i> -specific IgE-positive	25 (30.1%)	27 (33.4%)	0.65
- Equivocal (0.35-0.70 IU/ml)	15	8	
- Positive (0.71-3.50 IU/ml)	9	17	
- Strongly positive (3.51-17.50 IU/ml)	1	2	
Episodes of hospitalization	6 (prior to enrolment visit over last two years)	18 (admitted during the study period)	
PFT/Spirometry	Mild: 16	Mild: 10	0.33
	Moderate: 33	Moderate: 30	
	Severe: 22	Severe: 24	
	Very severe: 10	Very severe: 17	
Sputum Fungal Microscopy	07/21 samples showed septate hyphae	12/30 samples showed septate hyphae	0.61

Table 2: Hospitalizations in COPD patients with elevated serum *Aspergillus*-specific IgE levels

	COPD with high Total IgE and <i>Aspergillus</i> -specific IgE at follow-up (n=16)	COPD with high Total IgE and negative <i>Aspergillus</i> -specific IgE (n=37)	P value
Episodes of hospitalization in the study period	13	4	<0.001
No episodes of hospitalization	3	33	

Results and Discussion:

Of the 81 patients included in the study, 62 were males and 19 were females (M: F 3.3:1) with an age range of 45-82 years. Clinical presentation showed that 85% of the patients had productive cough while 46.9% had breathlessness at the time of study enrolment. Co-morbidities like hypertension (controlled with medication), arthritis and constipation were seen in 26 (32%) patients. Six (7.4%) patients gave a history of hospitalization in the last two years, though none had an exacerbation in the preceding three months. As per the guidelines from the National Institute for Health and Clinical Excellence (NICE), 16 (19.7%) patients were classified as mild (predicted FEV1 >80%), 33 (40.7%) as moderate (FEV1 50-79%), 22 (27.2%) as severe (FEV1 30-49%) and 10 (12.3%) as very severe COPD (FEV1 <30%). At the time of enrolment, increased levels of serum IgE were seen in 52 (64.2%) patients. Of these, 42 patients had serum IgE levels of 200-400 IU/ml while 10 had levels >400 IU/ml. *Aspergillus*-specific IgE was positive in 10 (12.3%) patients, of which nine had serum levels between 0.70-3.49 IU/ml and one had >3.5 IU/ml. Sputum samples were collected in 21 patients in the initial visit and 7 of them (33.3%) revealed septate fungal hyphae consistent with *Aspergillus* spp. At the follow-up visits, 18 patients (22.2%) reported instances of admissions during the study period. Reclassification as per the NICE guidelines showed 10 patients to have mild COPD, 30 as moderate, 24 as severe and 17 as very severe COPD. Of the 30 sputum samples collected on follow-up, 12 (40%) showed septate fungal hyphae. Serum samples in the follow-up visits showed positive serum total IgE in 52 patients. *Aspergillus*-specific IgE was positive in 27 (33.4%) patients in the follow-up visits (Table 1). Among patients with high serum total IgE levels, those with elevated *Aspergillus*-specific IgE showed frequent hospitalizations (P<0.001), as shown in Table 2. The correlation between *Aspergillus* sensitization and COPD severity has not been proven in the studies conducted till date. In five studies comprising more than 1000 patients, 13.6% of the COPD patients were found to have *Aspergillus* sensitization [9]. Another study reported 8.5-18% prevalence of *Aspergillus* sensitization in COPD patients [10]. In the present study, evidence of *Aspergillus* sensitization (raised *Aspergillus*-specific IgE) was seen in 30.1% patients at the time of enrolment. In the follow-up samples,

sensitization was evident in 33.4% of patients, though there was no statistical significance between the initial (summer months) and follow-up (winter months) visit. Reports on clinical significance of *Aspergillus* sensitization in COPD without asthma have provided conflicting results. Few studies have demonstrated a higher *Aspergillus* IgG and frequent *Aspergillus* sensitization in COPD patients than in controls [11]. *Aspergillus*-sensitized COPD patients have been shown to have worse FEV1 than non-sensitized patients, though other studies have not found similar results [8, 12]. A study also demonstrated that among patients admitted in intensive care units, COPD was one of the important predispositions for *Aspergillus* spp. Colonization or infection [13]. Another study by Guinea *et al.* showed a lower prevalence of *Aspergillus* spp in lower respiratory samples from COPD patients, however, 22% of these had features suggestive of invasive pulmonary aspergillosis [14]. A recent study by Wu *et al.* showed that *Aspergillus* colonization in COPD patients was associated with higher risk of acute exacerbation within three and six months after discharge from the hospital [15]. More recent study has reported a higher incidence of hemoptysis and prior history of tuberculosis in patients with COPD and chronic pulmonary aspergillosis [16]. In the present study, *Aspergillus* sensitization was detected in a higher proportion of COPD patients in follow-up visits (winter months) than time of enrolment (summer months), though the difference was not statistically significant. However, COPD patients with *Aspergillus* sensitization reported more frequent clinical exacerbations and hospitalizations. COPD patients often have impairment in ciliary function due to smoking [17] and frequent chest infections. This coupled with the neutropenia induced by corticosteroid treatment for exacerbations predisposes the COPD patients to *Aspergillus* colonization [18]. Luo *et al.*, in their recent study, revealed a significant correlation between *Aspergillus* sensitization and mucus plugging in COPD patients, both being harbingers of poor clinical outcome in COPD [19].

Conclusion:

We show a high prevalence of *Aspergillus* sensitization in patients with COPD that is independent of the seasonal variation. The frequency of clinical exacerbations and worsening

of symptoms was more frequent with *Aspergillus* sensitization. Thus, *Aspergillus* sensitization should be explored in COPD patients, especially in areas with favorable seasonal conditions for *Aspergillus* ubiquitousness.

Declarations:

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Conflict of interest:

The authors declare no conflict of interest.

Ethical approval:

The study was approved by the Institutional Ethics Committee, Kalpana Chawla Government Medical College, Karnal vide letter no. KCGMC/IEC/2021/106 dated 02.09.2021.

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