

Early Predictors of Asthma : Comparing Absolute Eosinophilic Count with IL-4 and IL-5

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ABSTRACT

Asthma is a chronic inflammatory disorder characterized by hyperresponsiveness and inflammation of conducting airways. It is a heterogeneous disease with different phenotypes based on clinical, functional or inflammatory parameters [1]. The disease presents with recurrent episodes of wheezing, tightness of chest and shortness of breath, with cough particularly in early morning.[2] Prevalence of the disease varies between 1-18 % of population in different countries with 300 million people affected worldwide [3,4]. It occurs at all ages and its prevalence has been increasing in developing countries. The disease increases health burden in the population, decreases productivity and causes considerable morbidity and mortality [5].

The clinical severity of asthma ranges from mild to severe. The common symptoms are usually due to variable bronchoconstriction causing limitation of airflow [6]. The disease is episodic in nature with increase in frequency and intensity over time. It can be triggered by viral infections, allergens, tobacco smoke, exercise, stress and drugs like aspirin, beta blockers and NSAIDS. Asthma is now hypothesized to be a T helper type 2 (Th2) inflammatory disorder with increase in the number of Immunoglobulin E (IgE) producing cells. The Th2-type cytokines, such as interleukin 4 (IL-4) and interleukin 5 (IL-5) are responsible for numerous effects important in bronchial asthma. IL4 has been implicated as the main cytokine involved and causes stimulation of mucus producing cells and fibroblasts, leading to airway remodeling [7-10]. Eosinophil is the main effector cell in allergic inflammation. IL-5 is the primary cytokine involved in in-vivo production, differentiation, maturation and activation of the eosinophils. Expression of IL-5 mRNA correlates with clinical indices of disease severity in asthma and the expression of IL 5 receptor in bronchial biopsies is more than 90% restricted to eosinophils.[11] Short-term treatment mainly consists of oral or inhaled corticosteroids (ICS). Long term medications include Anti-IgE and anticholinergic drugs which are useful in patients with severe asthma. Anti-IL5 (mepolizumab) and anti IL5R (benralizumab) medications are being offered to patients with severe uncontrolled eosinophilic asthma on high dose ICS. Anti-IL4R (Dupilumab) is also an option for these patients.

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METHODOLOGY

A hospital based descriptive cross-sectional study was conducted from March 2022 to May 2022, in 40 clinically diagnosed cases of Asthma, attending the Respiratory Medicine OPD at Lady Hardinge Medical College and associated Smt. Sucheta Kriplani Hospital, New Delhi. A detailed history and clinical examination was performed. Absolute eosinophil count (AEC) by fully automated Sysmax XN 1000 Hematology analyzer and Interleukin 4 and Interleukin-5 levels by Enzyme linked immunosorbant assay (ELISA) were done on all cases. All clinically diagnosed cases of asthma in the age group 18-40 years were included in the study. Those having a history of steroid intake for more than 14 days or having pre-existing lung (TB & congenital lung diseases) or cardiovascular disease or not willing to participate were excluded from the study. Written Informed Consent was taken from all the participants. Ethical clearance was taken from the Institutional Ethics Committee of Lady Hardinge Medical College and

associated Smt. Sucheta Kriplani Hospital, New Delhi.

RESULTS

Socio-demographics

The age of the participants included in the study ranged between 18 years to 60 years with mean age of 29.67 years. Maximum number of patients in age group 25-30 years, which constituted 25% of cases, followed by 22.5% cases in the age groups 20-25 and 30-35 years. There was a 1:1 male to female ratio among the participants with 20 males and 20 females.

AEC (Absolute Eosinophil Count) AEC of the patients varied from 80 cells/ μ l to 1670 cells/ μ l with mean value 553.57 cells/ μ l. Normal range is 30 cells/ μ l - 350 cells/ μ l. Values >450 cells/ μ l are considered Eosinophilia. 17/40 patients had Eosinophilia (42.5%). There was no statistically significant correlation of AEC with clinical severity of Asthma. (Table 1)

Table 1: Correlation of AEC with Clinical Severity

Clinical severity	Number of cases		p-value
	Normal AEC (<450 cells/ μ l)	Raised AEC (>450 cells/ μ l)	
Mild	20	15	0.464
Moderate	2	2	
Severe	0	1	

Table 2: Comparison of IL-4 with AEC 255.72ng/ml. Raised values of IL-4 were seen in 34/40 (85%) of total patients. The

IL-4 levels did not correlate with AEC. (Table 2)

	IL-4 (<200 ng/ml)	IL-4 (>200 ng/ml)
AEC (<450 cells/ μ l)	04	18
AEC (>450 cells/ μ l)	02	16

INTERLEUKIN-5 (IL-5)

IL-5 of the patients varied from 31.7 pg/ml to 82.45 pg/ml with mean value of 58.26 pg/ml.

Raised values of IL-5 were seen in 32/40 patients, 80% of total patients. There was no correlation of AEC with IL-5 levels. (Table 3)

Table 3: Comparison of IL-5 with AEC

	IL- 5(<50 pg/ml)	IL-5(>50 pg/ml)
AEC(<450 cells/ μ l)	04	18
AEC(>450 cells/ μ l)	02	16

DISCUSSION

In our study, 40 patients aged between 18 to 60 years participated, of which 20 (50%) were males and 20 (50%) were females. In our study we found that 35/40 (87.5%) presented as mild asthma 04/40 (10%) as moderate and 01/40 (2.5%) as severe asthma. No statistical significant correlation was found ($p < 0.464$) with Absolute Eosinophil Count. This could be due to the majority of patients being in the mild category and very few in moderate and severe groups. This distribution is different from the study conducted by Lalrinpuia et al [12]. They found 56% of mild cases, 24% of moderate cases and 10% of severe cases in their study and found clinical severity and Absolute Eosinophil count to have statistically significant correlation ($p < 0.01$). AEC levels were raised in 46% of patients in our study but did not show any statistically significant correlation with asthma severity ($p < 0.464$). The study conducted by Hameed et al [13] on 80 Iraqi children found that AEC level was high in all the Asthmatic children with mean of 413.11 cells/ μ l and there was statistical significant correlation ($p < 0.046$). Similarly, Lalrinpuia et al [12] found statistically significant correlation with p value < 0.01 severity of asthma and eosinophils. IL-4 levels were raised in 36/40 patients but there was no statistical significant correlation between IL-4 levels and AEC. Whereas, the study by Huan-zhong et al (14) found that IL-4 increases airway responsiveness by recruiting eosinophils into the airway in patients with allergic bronchial asthma with statistically significant correlation ($p < 0.01$). IL-5 levels were found raised in 32/40

patients, without any statistically significant correlation between IL-5 levels and AEC. In contrast to this, the study by Huan-zhong et al (14) found statistically significant correlation ($p < 0.01$) between IL 5 and AEC, indicating IL-5 mediated airway hyper-reactivity and airway eosinophilia. Most of the newly diagnosed cases of asthma in the present study had increased levels of IL-4 and IL-5 as compared to AEC, hence cytokines are more sensitive markers to detect asthma. However, a study should be conducted on more patients, especially in moderate and severe cases to understand the correlation better and to assess their role in management of asthma.

LIMITATIONS

As the study was conducted in only 40 patients, the results cannot be generalized accurately, therefore a larger study group should be studied as well. In addition, the study was a cross-sectional study, therefore the changes over the time and during the course of treatment could not be studied.

CONCLUSION

The present study included 40 newly diagnosed cases of asthma with 87.5% cases with mild, 10% cases with moderate and 2.5 % cases with severe asthma. The serum levels of cytokines IL4 and IL5 were evaluated in cases using ELISA and AEC (absolute eosinophil count) was analyzed by using Sysmex XN-1000. This study also evaluated the correlation of the cytokines levels with AEC. In the present study, all the

cases presented with respiratory problems, mostly at night or in early morning. 50% of the cases of male had exposure to pollution and roadside dust.

In both males and females, AEC was raised in 42.5% of the patients with values >450 cells/ μ l. 34/40 (85%) patients showed high levels of IL₄ i.e. more than 200 ng/ml. 32/40 (80%) both males and females showed high levels of IL₅ i.e. more than 50 pg/ml. These observations show

that IL-4 and IL-5 are sensitive and early biomarkers in Asthma as their levels were altered in 85% and 80% respectively of patients as compared to AEC levels (42.5%) which is currently used as a laboratory parameter in diagnosis and follow up of the patients. Moreover, their values are not affected by age or gender. However, these values did not show statically significant correlation with AEC and clinical severity of Asthma.

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