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INTERLEUKIN (IL)-17 AS A BIOMARKER IN ASSESSMENT OF BRONCHIAL ASTHMA SEVERITY

By

Eglal M. Kenawy , Hafez Abd El-Hafeez,
Nagwa Abd El-Ghaffar Mohamed* and Mahmoud M.A. Naeem

Internal Medicine Department, Faculty of Medicine - Al-Azhar University and
*Clinical and Chemical Pathology Department, National Research Center– Cairo

ABSTRACT

Background: Asthma is a serious global health problem affecting all age groups. Cytokines from T-helper 2 cells are believed to be critical contributors of asthma.

Objective: Measuring the serum levels of IL-17 as non-invasive biomarkers to assess asthma severity.

Patients and Method: A prospective case controlled study included forty patients were recruited from the outpatient clinic and inpatient of Internal Medicine Department, Al-Hussein University Hospital, Al-Azhar University divided into two equal groups (mild asthma and severe asthma) compared with twenty healthy non-smoker subjects. Total serum level of IL 17 and serum IgE was measured by ELISA technique. Complete blood count (CBC), pulmonary function tests (spirometry) and skin peak test were done for all patients.

Results: A significant increase in body mass index (BMI) and age were found in patients with severe asthma compared with those with mild asthma and normal control. Also, patients with severe asthma have more airflow limitation, with a higher serum level of IL-17, IgE, and the number of eosinophils than patients with mild asthma. Significant increase was found in the serum level of IL-17, IgE, the total count of WBCS the number of eosinophils and the number of platelets in asthmatic patients compared with normal control. IL17 has positively correlated with the serum level of IgE, the number of eosinophils, BMI, the age of patients, and negatively correlated with pulmonary function tests. By ROC analysis, a cutoff point for IL – 17 >51.5 Pg/ml, IgE >60IU/ml and the number of eosinophils >2.8% in the mild form of asthma, while the cutoff values for IL17>92.9Pg/ml, IgE>162.0IU/ml and the number of eosinophils >4.1%) in the severer form of asthma. Sensitivity, specificity and positive predictive value for IgE level in mild asthma were 85%, 80% and 77.8% respectively, while in severe asthma 65%, 85% and 83% respectively. Moreover, sensitivity, specificity, positive predictive values for IL17 in mild asthma were 97.5%, 100% and 100% respectively, while in severe asthma were 100%, 100% and 100% respectively.

Conclusion: Simple spirometric parameters (bedside test) were a good predictive tool for assessment asthma severity. Among laboratory tests, IL17 was the best biomarker for diagnosis and prediction of asthma severity in asthmatic patients than IgE.

Keywords: Asthma, IL17, IgE, eosinophils, obesity.

INTRODUCTION

Asthma is associated with increase morbidity and mortality with a prevalence rising up to 10% of the population in developed countries ***(Nanzer and Menzies-Gow, 2014).*** Asthma is charac-

terized by bronchoconstriction, airway hyperreactivity, inflammation, mucus hypersecretion, and remodeling of the airway. These processes are coordinated by a complex cytokine network ***(Ota et al., 2014).***

IL-17 is a one of this cytokine which enhances T-helper 2 (Th2) cell-mediated eosinophilic airway inflammation in asthma. Many studies were done to obtain the role of IL17 in asthma, one of them had demonstrated that inhibition of IL-17 can reduce antigen-induced airway inflammation, bronchial hyper-responsiveness and Th2 cytokine levels in animal models of asthma ***(Park and Lee, 2010).***

PATIENTS AND METHODS

Patients: Forty adult patients with asthma were recruited from the outpatient clinic and in-patient of Internal Medicine Department, Al-Hussein University Hospital, Al-Azhar University from 1/2015 to 6/2015. All patients were above the age of 18 years, nonsmoker asthmatic patients with variable severity with no other co-morbidities.

Patients have one or more of the following were excluded; concomitant infection, chronic obstructive pulmonary disease (COPD), gastro-esophageal reflux disease (GERD), liver disease, chronic rhinitis, malignancy, cystic ?brosis, interstitial lung disease, auto-immune disease and untreated cardiac failure. Asthmatic patients were classified according to GINA guidelines into mild persistent and severe persistent according to FEV1, frequency of symptoms, nocturnal symptoms and affection of exacerbations to sleep and activity. Patients were divided into two equal groups (20 patients in each group): **group 1:** (10 males and 10 females) with severe bronchial asthma; **group 2:** (10 males and 10 females) with mild bronchial asthma compared with 20 apparently healthy control 10 males and 10 females forming **group 3.**

Methods: All participants were exposed to the following after their consents: Full clinical examination, chest radiograph (chest X-ray and CT if needed to exclude other pathology), spirometry and allergy skin prick test (SPT).

Baseline spirometric study; including forced vital capacity (FVC), Forced expiratory volume in first second (FEV1), (FEV1/FVC) ratio and peak expiratory flow (PEF) **(MiniSpir, MIR S.r.l. via Del Maggiolino 125, 00155 Roma – Italy).** All pulmonary function data were expressed as percent of predicted value. The FEV1/FVC ratio is normally greater than 0.75 to 0.80 and a reduced ratio of FEV1 to FVC indicates airflow limitation

Assessing the SPT; Positive and negative controls were measured first. The negative control excluded. The largest diameter of the wheal of each particular test is measured, a positive being a wheal

of ≥ 3 mm in diameter ***(Heinzerling et al., 2014)***.

Laboratory Work:

Laboratory investigations included: Complete Blood Count (CBC) esp. eosinophilic count, total serum IgE and serum Interleukin (IL)-17.

Five mls of venous blood samples were taken from each subject participating in the study and divided into aliquots: The 1st aliquot about 1.5 mls of venous blood was added to tube containing EDTA for determination of complete blood picture on coulter counter T890 (coulter counter, Harpenden, UK). The 2nd aliquot was 3.5 ml was left to clot and then the serum was separated by centrifugation at 1000g for 15 min and stored at -20°C for determination, total IgE and IL-17.

The Serum IgE was measured by quantitative sandwich ELISA and the kit was supplied by Abcam (330 Cambridge Science Park, Cambridge, UK) ***(Mehmedović et al., 2012).***

The human IL-17A ELISA is an enzyme-linked immunosorbent assay for the quantitative detection of human IL-17A. The kit was supplied from IBL International GmbH **(Flughafenstr. 52A, 22335 Hamburg, Germany)** ***(Karabulut et al., 2016).***

Statistical analysis: Data were statistically analyzed using statistical package for social sciences (SPSS) version 23.0 for windows. Data are presented as the Mean ± standard deviation (SD), frequency, and percentage. Categorical variables were compared using the chi-square ($\chi 2$). Continuous normally distributed variables were compared using One Way Analysis of Variance (ANOVA) followed by post hoc analysis using LSD test. Pearson correlations coefficients were used to assess the bivariate correlations between variables. A receiver operating characteristic (ROC) curve analysis was performed. The area under the curve (AUC) was also used to determine the ability of IgE, IL17 levels to diagnose asthma severity. The level of significance was accepted if the P value < 0.05.

RESULTS

Sixty subjects, 30 were males and 30 females, were classified into three groups 20 patients with severe asthma, 20 patients with mild asthma, and 20 normal subjects were taken as control, with mean age of the studied sample was 27.03±7.48 years and body mass index (BMI) 25.22±3.09 (Table 1).

Table (1): Demographic characteristics of the studied groups**.**

Variable	**No. (N= 60)**	**%**
Group	20	33.4
Severe asthma	20	33.3
Mild asthma		
Control (non asthmatic)	20	33.3
Gender	30	50.0
Male		
Female	30	50.0
Age (Years) (M ± SD)	27.03 ± 7.48	
BMI (kg/m^2) (M ± SD)	25.22 ± 3.09	
Occupation		
Student	7	11.7
Housewife	14	23.3
Manual worker	5	8.3
Marketer	3	5.0
Carpenter	1	1.7
Concierge	1	1.7
Dealer	1	1.7
Teacher	1	1.7
Farmer	2	3.3
Mechanic	1	1.7
Seller	2	3.3
Technician	1	1.7
Driver	1	1.7
House officer	5	8.3
Physician	5	8.3
Nurse	10	16.7

A significant increase in age and body mass index (BMI) were found in patients with severe asthma compared with those with mild asthma $p < 0.001$ and $p < 0.0013$ respectively and normal control $p < 0.001$ and $p < 0.001$ respectively. A non-significant statistical difference in the age and BMI between patients with mild asthma and normal control group were found, $p=0.490$ and $p =0.090$ respectively. Significant elevation in serum level of IL 17, IgE, total white blood count (WBC), eosinophils and platelet were found between patients and normal control with

P values < 0.001, 0.001 0.027, 0.001 and 0.020 respectively. Also, the significant increase in serum level of IL17, IgE and eosinophils in patient with severe asthma than those with mild asthma were found with P values < 0.001, 0.001 and 0.001 respectively. Comparing spirometric parameters of patients with normal control, we found a limitation of airflow in patients than the normal control with p - value for FVC%, FEV%, FEV1/FVC and PEF were 0.001, 0.001, 0.001 and 0.001 respectively, with more airflow limitation in severe asthmatic patients than those with mild asthma p value of FVC%, FEV%, FEV1/FVC and PEF were 0.001, 0.001, 0.001 and 0.001, respectively (Table 2).

Table (2): Some demographic and laboratory data for the three studied groups.

Variable	Mild asthma (N=20)	Severe asthma (N=20)	Normal control (N=20)	One Way ANOVA		Post hoc analysis by LSD test		
	Mean ±SD	Mean ±SD	Mean 0±SD	F	P-value	P1	P2	P3
Age (Years)	24.25 ± 2.50	32.05 ± 8.82	24.80 ± 2.50	12.593	0.001	0.490	0.001	0.001
BMI (kg/m2)	24.80 ± 2.52	27.29 ± 3.44	23.56 ± 1.95	9.847	0. 001	0.090	<0.001	0.013
IL – 17 (Pg/ml)	68.29 ± 13.63	130.97 ± 20.96	34.10 ± 6.91	215.228	0. 001	<0.001	<0.001	<0.001
T. IgE (IU/ml)	111.33 ± 92.50	400.95 ± 327.97	52.65 ± 62.09	17.390	0. 001	0.024	<0.001	0.001
HB (g/dl)	13.41 ± 1.01	13.93 ± 1.06	13.63 ± 1.12	1.203	0.308	0.518	0.399	0.121
WBCs ($X10^3/mm^3$)	7.75 ± 1.33	7.75 ± 1.75	6.50 ± 1.81	3.884	0.027	0.017	0.032	1.000
Eosinophil %	4.60 ± 1.64	7.31 ± 2.75	2.22 ± 1.04	34.337	0. 001	<0.001	<0.001	0.001
Platelets ($X10^3/mm^3$)	283.15 ± 51.78	275.20 ± 59.02	237.00 ± 50.60	4.186	0.020	0.007	0.034	0.653
FVC %	95.20 ± 6.22	68.55 ± 13.15	99.95 ± 6.96	66.092	0. 001	0.028	<0.001	<0.001
FVE1 %	68.95 ± 3.68	33.60 ± 7.36	99.15 ± 12.11	301.285	0. 001	<0.001	<0.001	<0.001
FEV1/FVC	70.85 ± 2.87	49.20 ± 6.94	98.40 ± 9.23	257.665	0. 001	<0.001	<0.001	<0.001
PEF %	64.60 ± 2.70	33.10 ± 9.61	97.80 ± 14.75	197.998	0. 001	<0.001	<0.001	<0.001

P1: Mild vs control; P2: Severe vs control; P3: Mild vs severe.
BMI: body mass index; IL - 17: Interleukin – 17; T. IgE: Total IgE; HB: Hemoglobin%; WBCs: White Blood Cell**s.**
FVC: Forced Vital Capacity; FVE1: Forced Expiratory Volume in 1 Second; FEV1/FVC: the ratio of FEV1 to FVC; PEF: Peak Expiratory Flow

Serum level of IL17 was positively correlated with severity of asthma, serum level of IgE, number of eosinophils, BMI, age were p<0.001, 0.001, 0.001, 0.004 and 0.001 respectively, and negatively correlated to spirometric parameters FVC%, FVE1%, FEV1/FVC%, PEF% with P<0.001 for all (Table 3).

Table (3): Correlation the IL–17 level with some laboratory, spirometric, demographic data.

IL-17 (pg/ml) / Variables	IL – 17 (Pg/ml)	
	r	**p**
T. IgE (IU/ml)	0.589	**0.001**
HB (g/dl)	0.138	0.216
WBCs ($X10^3/mm^3$)	0.070	0.529
Eosinophil %	0.785	**0.001**
Platelets ($X10^3/mm^3$)	– 0.017	0.880
FVC %	– 0.510	**0.001**
FVE1 %	– 0.560	**0.001**
FEV1/FVC %	– 0.524	**0.001**
PEF %	– 0.663	**0.001**
BMI (kg/m^2)	0.317	**0.004**
Age (years)	0.610	**0.001**

A number of atopic patients in mild asthmatic group was 11 (55.0%), while in severe asthmatic, atopic patients 7 (35%) with p< 0.522 (Table 4).

Table (4): Comparison of skin prick test in twenty patients with mild asthma compared with twenty patients with severe asthma.

Skin prick test / Severity of Asthma		Severity of Asthma		*p*
		Severe (N = 20)	**Mild (N = 20)**	
Skin prick test	Negative	7 (35.0%)	11 (55.0%)	0.522
	Aspergellus. F	3 (15.0%)	2 (10.0%)	
	Tobacco	4 (20.0%)	4 (20.0%)	
	House dust	0 (0.0%)	1 (5.0%)	
	Mixed pollen	1 (5.0%)	0 (0.0%)	
	Mites	0 (0.0%)	1 (5.0%)	
	Cockroach, Mites	1 (5.0%)	0 (0.0%)	
	Candida	1 (5.0%)	0 (0.0%)	
	Aspergellus. F & Tobacco	1 (5.0%)	0 (0.0%)	
	Aspergellus. F & Mites	1 (5.0%)	0 (0.0%)	
	Tobacco & house dust	1 (5.0%)	0 (0.0%)	
	Mixed pollen & house dust	0 (0.0%)	1 (5.0%)	

By ROC analysis of data we found a cutoff point for IL – 17, IgE and number of eosinophils in the mild form of asthma (>51.5 Pg/ml, >60IU/ml and >2.8% respectively), while the cutoff values for IL17, IgE and number of eosinophils in the severe form of asthma were (>92.9Pg/ml, >162.0 IU/ml and >4.1% respectively). The sensitivity, specificity and positive predictive value for IgE level in mild asthma were 85%, 80%, and 77.8% respectively, while in severe asthma were 65%, 85% and 83% respectively.

Moreover, the sensitivity, specificity and positive predictive value for IL17 in mild asthma were 97.5%, 100% and 100% respectively, while in severe asthma were (100%, 100% and 100%) respectively. The sensitivity, specificity and positive predictive value for IgE level in mild asthma were 85%, 80%, and 77.8% respectively, while in severe asthma 65%, 85% and 83% respectively. Moreover, the sensitivity, specificity and positive predictive value for IL17 in mild asthma were 97.5%, 100% and 100% respectively, while in severe asthma were 100%, 100% and 100% respectively.

DISCUSSION

Cytokines from T-helper 2 cells are believed to play a critical role in asthma. In the last few years, IL-17, one of T-helper lymphocyte-associated cytokine had been considered as another potentially important mediator of asthma ***(Silverpil and Lindén, 2012).***

Many studies were done on patients with asthma to categorize them into a different cluster, phenotypes to obtain a clear picture for the patients with severe form of asthma. ***Moore and his coworker (2010)*** made an algorithm approach to obtain 5 clusters for the classi?cation of disease severity. While ***Dursun and his Colleagues (2014)*** stated that current phenotyping proposals failed to cover all severe asthma (SA). Thus, there is still need further investigations in order to explore validity and applicability of phenotyping of SA. Furthermore ***Loureiro and his Colleagues (2015)*** were con?rmed many results of Moore et al by using a biomarker and found other parameters of interest such as age, weight, blood eosinophilia. We found a significant increase in serum level of IL-17 and IgE in asthmatic patients than control group while those with a higher serum level of IL17, and IgE had a severe form of asthma than other patients with asthma. Various studies have reported the expression of IL-17 and IgE was higher in patients with bronchial asthma than that of healthy control ***(Chen et al., 2010; Lu et al., 2012; Robinson et al., 2013; Fn, 2016; Lv et al., 2016)***. However, an increased immunoglobulin E (IgE) production was reported by other's ***(Zeiger and Heller, 1995; Thomas et al., 2003;Skiepko et al., 2009; Heidenfelder et al., 2010)*** to be the strongest predisposing factor for the development of asthma and significantly correlated with allergy as determined by the serum IgE levels, while other researchers found a negative association between IgE and spirometric parameter (FEV1, FVC, FEV1/FVC) in asthmatic patients than healthy control ***(Anupama et al., 2005; Satwaniet al., 2009; Mojtaba et al., 2011).*** Moreover, ***Rotsides and his coworkers (2010)*** were found a high positive association between increased

IgE and asthma severity in children and concluded that serum IgE level is a strong predictor for allergy in asthmatic children.

Other studies have reported that increased serum IL-17 level as an independent risk factor for severe asthma. One possibility is that IL-17 could induce the release of the inflammation factor IL-6 to cause neutrophil recruitment and activation related to local inflammation of the lungs ***(Sandeep et al., 2010; Agache et al., 2010)***. Also, the increase of IL-17 in SA compared with other forms of asthma was found by ***Alyasin and his coworkers (2013)*** suggest that it can be used to predict asthma severity in children.

A numerous number of eosinophils can be found in the bronchial airway in eosinophilic asthma phenotype, and this phenotype can be identified by peripheral eosinophil count ***(Possa et al., 2013).*** Interleukin-17 (IL-17) is an early trigger of the T lymphocyte-induced inflammatory response and can induce and activate the neutrophil recruitment to the respiratory tract ***(Qu et al., 2013)*** and also enhances T-helper 2 (Th2) cell-mediated eosinophilic airway inflammation in asthma ***(Park et al., 2010).***Moreover, In non-allergic eosinophilic asthma, stimulation of epithelial air way by microbes, pollutants and glycolipids leading to release of epithelium-derived cytokines IL-33, IL-25 and thymic stromal lymphopoietin .This cytokines well stimulate and activate the innate lymphoid cells (ILCs) via the (IL-17 receptor and this lead to produce high amounts of IL-5 and IL-13 from the (ILCs) leading to eosinophilia, mucus hypersecretion and airway hyperreactivity. ***(De Groot et al,2015).***

We found increased level of IL17 was positively correlated to number of eosinophils, many previous researchers linked between increased level of IL17 and increase number of neutrophils like ***Sven and his colleagues (2015).*** While, ***Hawas and his colleagues (2009)*** was found levels of sputum IL 17 and serum FAS were increased in bronchial asthma patients especially in severe asthma with decrease in eosinophils apoptotic ratio in bronchial asthma patients than healthy controls***. Doe and his colleague (2010)*** was found a potential role for the Th17 cytokines IL-17A and IL-17F in asthma and COPD but did not demonstrate a relationship with neutrophilic in?amma-tion·

Moreover, we observe a great variability in the serum level of IgE among patients in the same group (atopic patients had a higher level than non-atopic). According to the values obtained from rock analysis, we suggest that serum IL17 is a good biomarker for diagnosis and prediction of asthma severity among atopic and non-atopic patients.

Also, we showed that the age and BMI of patients with severe asthma were significantly elevated than patients with mild asthma and control group which can be explained by aging increases morbidity in patients with asthma. The pathogenesis of adult-onset asthma are linked to several metabolic and inflammatory components which are common in other diseases like, diabetes mellitus type 2 (DM2), cardio-vascular diseases (CVD), obesity, metabolic syndrome (MBO) and psychiatric diseases. In younger age groups, allergy and obesity are the most comorbidity associated with asthma

(Kankaanranta et al., 2016). A meta-analysis has been performed to evaluate the obesity as a risk factor for asthma and reviled that the risk was 1.20 for overweight and 1.43 for obese men. The corresponding risk estimates for women were 1.25 for overweight and 1.78 for obesity ***(Guh et al., 2009)***. Anther US epidemiological study was done and reported odd ratio 1.29 for obese males and 1.55 for obese females whom can developed asthma in comparative with normal weight populations ***(Wang et al., 2015).***

Mohanan and his Colleagues* (2014); *Baffi and his Colleagues (2015) explained why asthma develops more frequently in obese than non-obese. This may due to potential contributing factors include changes in airway function due to the effects of obesity on lung mechanics; systemic inflammation through the release of pro-inflammatory cytokines in obesity ***(Sideleva and Dixon, 2014)*** and an increased prevalence of co-morbidities, genetic, developmental, hormonal via adipocyte-derived hormones (adipokines), which have immunomodulatory effects ***(Sideleva et al., 2013)*** *or* neurogenic influences or by increasing oxidative stress ***(Sideleva et al., 2012). Kim and his Colleagues (2014)*** were found in an experimental obese mouse that obesity causes airway inflammation and airway hyper-reactivity associated with an expansion of pulmonary IL-17+ ILC3 cells.

Also, our study showed a significant increase in the platelet count in the bronchial asthma groups compared with normal subjects. Experimental evidence suggested that platelets have a role in each stage of asthma pathogenesis in the development of bronchoconstriction, airway inflammation, and airway remodeling. Platelets have the ability to undergo chemotaxis, releasing various important mediators, expressing adhesion molecules on their surface and becoming activated in response to mediators released by other cells ***(Kornerup and Page, 2007).*** Also, ***Benton and Coworkers (2010)*** showed a significant association between platelet and eosinophil activation in airways of human subjects with asthma.

CONCLUSION

Simple spirometric parameters (bedside test) are a good predictive tool for assessment asthma severity. Among laboratory tests, IL17 is the best biomarker for diagnosis and prediction of asthma severity in atopic and non–atopic asthmatic patients than IgE.

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إنترلوكين - ١٧ كدليل حيوي غير نافذ في تقييم شدة الربو الشعبي

إجلال محمد محمد قناوي - حافظ أحمد عبد الحفيظ - نجوي عبدالغفار محمد* - محمود محمد نعيم

قسم الباطنة العامة بكلية الطب – جامعة الأزهر ، * قسم الباثولوجيا الإكلينيكية والكيميائية- المركز القومى للبحوث

مقدمة البحث: الربو هو مشكلة صحية عالمية خطيرة تؤثر على جميع الفئات العمرية. ويعتقد أن السيتوكاين الناتج من الخلايا التائية لها دور حاسم في الربو الشعبي. ففي السنوات الأخيرة، يعتبر إنترلوكين-١٧ (وهو احد هذه السيتوكاين المرتبطة بالخلايا التائية اللمفاوية) وسيطا هاما في الربو الشعبي.

الهدف من البحث: يهدف البحث إلى قياس نسبة الإنترلوكين-١٧ في الدم كمؤشر حيوي غير نافذ لتقييم شدة الربو الشعبي.

المرضى وطرق البحث: تضمن البحث ثلاث مجموعات: عشرون مريضا بحساسية صدر شديدة، وعشرين مريضا بحساسية صدر متوسطة، وعشرين شخصاً طبيعيا كمجوعة حاكمة، وتم اخذ المرضى من العيادة الخارجية والقسم الداخلي لقسم الأمراض الباطنة بمستشفى الحسين الجامعى بجامعة الأزهر فى الفترة من يناير ٢٠١٥ الى يونيو ٢٠١٥.

اشتملت خطة البحث على تقييم جميع المرضى كالآتى: أخذ التاريخ المرضى الكامل، الفحص الإكلينيكى، وعمل وظائف التنفس، صورة دم كاملة، وقياس نسبة الأجسام المناعية المضادة بالدم، وقياس معدل الإنترلوكين-١٧ في الدم.

نتائج البحث: أظهرت النتائج وجود إرتباط كبير بين فرط إستجابة مجرى الهواء وبين نسبة الأجسام المناعية المضادة مع إرتفاع معدل الإنترلوكين-١٧ في مرضي الربو الشعبي. كما أظهرت النتائج أن قياس معدل الإنترلوكين-١٧ في الدم يمكن استخدامه للتشخيص والتنبوء بشدة الربو الشعبي .

الخلاصة: عمل وظائف التنفس للمرضى من الأشياء المهمة والسهلة لتعيين شدة الربو الشعبى كما أن تعيين نسبة الإنترلوكين فى الدم من التحاليل السهلة والدقيقة التى تساعد على التشخيص والتنبوء بشدة الربو الشعبى.