

Study of serum interleukin-12 and total serum immunoglobulin-E in relation to bronchial asthma severity in childhood

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Abstract

Bronchial asthma is a major public health concern affecting 100-150 million people worldwide. Elevated total serum immunoglobulin E (IgE) is considered as an objective marker of allergy and has been associated with a number of respiratory disorder. Interleukin-12 (IL-12) is a key cytokine involved in regulating the balance between TH1 and TH2 cells by promoting TH1 response. Reduced capacity to produce this cytokine could lead aberrant TH2 development. The objective in this to find if any correlation between serum IgE level and serum interleukin-12 with severity of bronchial asthma for both the definitive diagnosis and the therapeutic strategy. A total of fifty patients with age 12 years and below (28 males and 22 females) and twenty five of case controls with matched age and sex were randomly selected from apparently healthy individuals from January to June of 2010 who were attending the outpatient department in Kerbala teaching pediatrics hospital with symptoms suggestive of bronchial asthma. The patients who were not on any anti asthma medication in previous one week were included in the study. Blood sample was taken from each patient at time of attending , sera were separated and kept frozen at -20°C until used. Serum interleukin -12 and total IgE levels were done by solid phase enzyme -linked immunosorbent assay (ELISA). A significant decrease of serum levels of IL-12 was found in bronchial asthmatic children compared with normal controls. This significant decrease of IL-12 was observed in sever asthmatic patients compared with mild and moderate cases. However there is increase of mean serum total IgE in bronchial asthmatic children compared to healthy control groups. mean serum IgE levels were increased as the severity of asthma increased. The present study suggested that the increased serum total levels IgE in bronchial asthmatic patients beside decreasing the serum interleukin-12 could be considered as a key component in bronchial asthma pathogenesis and hence their therapeutic manipulation may be help in bronchial asthma management.

دراسة الانترلوكين 12 والغلوبولين المناعي نوع E وعلاقتها في شدة الربو القصبي عند الأطفال

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الخلاصة

ان الربو القصبي من الأمراض الرئيسيه في الصحة العامة يُؤثر على حوالي 100-150 مليون شخص حول العالم. ان تركيز المصل الكلي للغلوبولين المناعي نوع E يعتبر كعلامة موضوعية من الحساسية وكذلك مرتبط به عدد من الأمراض التنفسية. انترلوكين - 12 له دور رئيسي للمشاركة في تنظيم التوازن بين الخلايا المناعية المساعدة الأولى والثانية. ان أي انخفاض في انتاج انترلوكين 12 قد يؤدي الى زياده قدره الخلايا المناعية المساعدة الثانية وبالتالي يفقد التوازن بين الخليتين . ن الهدف من هذه الدراسه هو لايجاد علاقه بين مستوى الانترلوكين 12 الغلوبولين المناعي نوع E مع الربو القصبي للاطفال من حيث فائده لتشخيص مرحله المرض وللعلاج . شملت الدراسه 50 طفل مصابين بالربو القصبي واعمارهم من حوالي 12 سنه فمادون بالاضافه الى 25 طفل سليما انضموا الى الدراسه لغرض المقارنه كمجاميع ضابطه. تمت الدراسه في مستشفى كربلاء التعليمي للاطفال للفترة من كانون الثاني لغايه حزيران لسنه 2010 هـ. تمت الدراسه في تشخيصهم حسب الاعراض السريرييه من قبل اخصائي الاطفال وقد تم التاكد بانهم لم يتعاطوا أي علاجات ضد الحساسيه قبل سحب الدم لهم . وباستخدام تقنيه الـ EIA تم قياس الغلوبولين المناعي نوع E والانترلوكين 12 . كشفت الدراسه على ان هنالك انخفاضاً معنوياً في مستويات الانترلوكين 12 وارتفاعاً في مستويات الغلوبولين المناعي نوع E في المرضى المصابين بالربو القصبي مقارنة بالاطفال الاصحاء. ولوحظ ايضاً هنالك علاقه بين الانترلوكين 12 والغلوبولين المناعي نوع E وشده المرض . حيث وجد قله في تركيز الانترلوكين 12 مع الدرجه الحاده للمرض اذا قارنا بالحاله الخفيفه والمعتدله للمرض . على العكس من ذلك المستويات المصلية للغلوبولين المناعي E قد سجل ارتفاعاً معنوياً في شده المرض . ونتيجة للاعتبارهم المكون الرئيسي في التسبب للربو القصبي أي تغيرات في نسبهم قد يفيد في الكشف عن مرحله شده المرض و العلاج له .

Introduction

Bronchial asthma is a type I hypersensitivity reaction where combination of allergens with serum immunoglobulin E (IgE) antibodies produces the airway inflammation and asthmatic symptoms⁽¹⁾

IgE is a trace glycoprotein and normally accounts for less than 0.001% of total serum immunoglobulin. The concentration of IgE in serum is age dependent and normally remains at levels less than 10 IU/ml in most infants during the first year of life. ⁽²⁾

Allergic disease including asthma are characterized by increase of serum

immunoglobulin E (IgE) levels . Several studies reveal that IgE ,through its high affinity IgE receptors(Fc epsilon R1),is a critical regulator of Th2 responses⁽³⁾

Interleukin 12(IL-12) is derived from monocytes and macrophages but also B cells, dendritic cells ,Langerhans cells polymorphonuclear neutrophils (PMNs),and mast cells . The biological active forms a heterodimer .The larger subunit (p40) is homologous to the soluble receptor for IL-6, whereas the smaller subunit (p35)is homologous to IL-6. ⁽⁴⁾

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IL-12, is known to be a potent inducer of IFN- γ production, and its co administration has been shown to inhibit IgE production. IL-12 is characterized as a heterodimeric cytokine induces cell-mediated immune functions, up regulates TH1 cytokines and inhibits or down regulates Th2 cytokines.^(5,6)

Therefore ,the objective of this study is to investigate the changes of serum levels of IL-12 and IgE in bronchial asthmatic children in relation to clinical asthma severity .

Patients and methods

A total of 50 patients with bronchial asthma (28 male and 22 female), with a mean age (6.6 ± 3.38) years, age range (1 -12) years referred to outpatient department in Kerbala teaching pediatrics hospital with symptoms suggestive of bronchial asthma. The patients who were not on any anti asthma medication in previous one week were included in this study. Patients name ,age sex and duration of symptom were noted.

Severity of bronchial asthma was classified according to NAEPP Guidelines (National Asthma Education and Prevention Programme)⁽⁷⁾ into :

1- mild bronchial asthma :symptoms less than once week ,with

Recently, great progress has been made in elucidating the role of helper T (TH) cells through its cytokine profiles in allergic diseases. Type 1 (TH1) cells synthesize interferon (IFN) γ , inhibit IgE responses, and block the development of type 2 (TH2) cells. TH2 cells produce interleukin (IL)-4 and IL-13, which stimulate the production of IgE.

exacerbations ;nocturnal symptoms not more than twice a month .

2- moderate bronchial: asthma symptoms daily; exacerbations may affect activity and sleep.

3- sever bronchial asthma :symptoms daily with frequent exacerbations ; frequent nocturnal symptoms .Age and sex matched 25 healthy controls. Solid phase enzyme -linked immunosorbent assay (ELISA) were used for estimation of IL-12p40(BioSource Europe S.A Rue de l'Industrie,8,B-1400 Nivelles, Belgium)and total IgE (DRG International Inc.,USA).

Results

As shown in table (1), A total of fifty patients with bronchial asthma (28 males and 22 females), their age ranged from (1 -12) years with a mean age (6.6 ± 3.38) years were included in the study. In addition, twenty five healthy subjects who were age matched to the patients group were also included as a healthy control group.

In addition a cases of bronchial asthma, patient' severity of disease was classified according to NAEPP Guidelines for bronchial asthma to mild ,moderate and sever .Therefore, the present study classified bronchial asthma into three groups: (21) with mild bronchial asthma ,(18) moderate and (11) sever bronchial asthma.

As shown in table(2) the mean serum in bronchial asthma children as compared to healthy controls($P<0.001$)(95.2 ± 24.3), (148.68 ± 29) respectively, while higher mean total serum IgE values were observed in comparison to healthy control groups (273.2 ± 231.7), (93.76 ± 22) respectively.

The statistical analysis also revealed that there are a negative correlation between serum level of IL-12 and total

level of IL-12 was decrease

Table (3) shows the mean levels of IL-12 were lower in patients with severe disease compared to patients with mild and moderate bronchial asthma ($p<0.001$). On contrary, total serum IgE levels were higher in patients with severe diseases compared with mild and moderate.

serum IgE in bronchial asthmatic children ($p<0.001$), $r=-0.77$).

Table(1): The distribution of studied samples according to age and gender

Parameters		Groups	
		Healthy control N= 25	Bronchial Asthma patients N=50
Age(years) X \pm SD		6.88 \pm 3.71	6.6 \pm 3.38
Range		1 -13	1-12
Gender	Male	14 (56 %)	28(56%)
	Female	11 (44 %)	22(44%)
	Total	25(100%)	50(100%)

Table (2):Serum levels interleukin-12(pg/ml) and total immunoglobulin- E(IU/ml) of bronchial asthma patients in comparison to the apparently healthy control.

Groups	Parameters	
	IL-12	Total IgE
Bronchial asthma (N=50)		
Mean \pm SD	95.2 \pm 24.3 *	273.2 \pm 231.7 *
Range	45-130	44-790
Healthy controls(N=25)		
X \pm SD	148.68 \pm 29.0	93.76 \pm 22.0
Range	60 -195	15-130

***P<0.001**in compared to healthy control .

Table(3):Comparison of serum IgE level(IU/ml) and interleukin-12p40 level(pg/ml) with severity of bronchial asthma .

Groups of bronchial asthma	No.	IL-12 X \pm SD	IgE X \pm SD
Mild	21	109 \pm 24**	97 \pm 44***
Moderate	18	104.6 \pm 10	276.1 \pm 123
Severe	11	53.6 \pm 5*	604.9 \pm 217*

* **p< 0.001** in compared to mild and moderate .

****p> 0.05** in compared to moderate.

*** **p< 0.001** in compared to moderate.

Discussion

Bronchial asthma is chronic airway inflammation characterized by episodes of reversible airway obstruction , IgE production , increased mucus secretion ,and an airway infiltrate with eosinophilic granulocytes ,mast cells and lymphocytes. ⁽⁸⁾.airway inflammation is caused by a defect in immune regulation involving T helper lymphocytes , with an increase in T- helper 2(Th-2) lymphocytes and a compensatory decrease in T-helper 1(Th-1) ⁽⁹⁾.

In the last decade , one of the most striking advances in the study of bronchial asthma has been the recognition that cytokines including IL-2,IL-4,IL-5,IL-12 and IL-18 have integral roles in orchestrating ,perpetuating and amplifying the underlying processes in this disease. Future therapy for bronchial asthma may involve specific targeting of the cytokines rather than global immunosuppression. ⁽¹⁰⁾

Therefore the present study analyzed serum levels of IL-12 and total serum IgE as indicators of the immunoresponse in children with bronchial asthma.

Result in the current study showed a significant elevation level of the serum total IgE which associated with a significant lower values of serum IL-12 of bronchial asthma patients when compared with control group.

These observations are in accordance with the previous results reported by *Zedan et al* ⁽¹¹⁾.and *Satwani et al* ⁽¹²⁾ who found that children with bronchial asthma display elevated level of serum IgE and decrease level of IL-12 when compared with healthy donors . In both studies , the decrease of Th1 cytokines such as IL-12 is lower than that seen for Th2 cytokines in immunopathogenesis of bronchial asthma ,possibly through the inhibition of Th1 lymphocytes .

In the other hand the result obtained from the present study are in contrast to that reported by *Sultnova et al* ⁽¹³⁾ who found an elevated serum IL-12 in bronchial asthma patients .As well as in disagreement with *Shima* and *Ando* ⁽¹⁴⁾ who reported that serum IL-12 level in children were not associated with allergic symptom while serum IL-18 level were significant higher in children who had asthma .

Moreover the present study assess the association of serum levels IL-12 and IgE to degree of severity and hence disease progression according to NAEPG Guidelines for asthma.

Result in the current study showed a significant negative correlation was found between different degrees of bronchial asthma severity and serum IL-12 whereas ,the increase serum IgE levels in regard to clinical severity of asthma .

The present and previously reported result ,could be further supported by the findings of *Naseer et al*⁽¹⁵⁾ who reported that IL-12 is significantly reduced in peripheral blood and in airway biopsy specimens in comparison with healthy controls, they found that patients with bronchial asthma following treatment with corticosteroids had increased IL-12 mRNA levels in biopsy specimens ,and although the administration of IL-12 has failed to show any effects on bronchial asthma with mild degree.

This findings are in consistent with *Meyts et al*⁽¹⁶⁾ whom reported that patients with bronchial asthma had decrease level of IL-12 and increase level in IgE with sever and moderate of bronchial asthma, and explanation to that may be IL-12 induced cell mediated immunity by up regulating Th1 cytokines especially interferon gamma (IFN- γ) which inhibit IgE production with allergic disease ,(IFN- γ) is proinflammatory cytokine, that play an important role in Th1 cell activation .IL-12 has been shown to directly inhibit Th2 cytokines function by IFN- γ independent mechanism ,also *Gavett et al*⁽¹⁷⁾ demonstrated in mouse model that IL-12 effectively suppressed inflammatory air way hyper responsiveness that was included by repeated antigen challenge.

Conclusion The study concluded that decreased serum IL-12 level production beside increasing total serum IgE level in bronchial asthmatic children could be considered as a key component in

bronchial asthma pathogenesis and hence their therapeutic manipulation may be of help in bronchial asthma management.

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