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الآليات المناعية للخلايا التائية TH2 في الأشخاص المصابين بالشرى

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The Immunological Mechanisms of TH2 in Urticarial People

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الخلاصة

إن إنتاج IgE وإطلاق المواد من الخلايا البدينة هما عاملان مهمان في ظهور وتطور الشرى، ولكن هناك تفاعل معقد بين السيتوكينات يؤثر على استمراريته. إن إنترلوكين-٤(IL-4) ، المرتبط باستجابات خلايا T المساعدة ٢، هو عامل حاسم في المناعة المرضية للشرى. لذلك، يسلط هذا العمل الضوء على دور خلايا Th2في تطوير الشرى من خلال تحديد مستويات اثنين من علامات المناعة الخاصة بهم IL-4 :و IgE لدى المرضى العراقيين. الطرق: تم تضمين ثمانية وثمانين موضوعًا في هذا العمل، كان ٤٨ منهم مرضى بالشرى و ٤٠ كانوا أصحاء. تم استخدام جهاز AFIAZ-10 الأوتوماتيكي بالكامل وبروتوكول ELISA لقياس مستويات الأجسام المضادة IgE الكلية و IL-4. النتائج: أظهرت النتائج الحالية مستويات أعلى من إجمالي IgE والأجسام المضادة IL-4 لدى المرضى مقارنةً بمجموعه الاصحاء، وكان هناك ارتباط إيجابي كبير(R=0.748 ، (P<0.01 بين مستوياتها لدى مرضى الشرى. علاوة على ذلك، أشارت نتائج اختبار ROC إلى أن إجمالي IgE هو علامة حيوية دقيقة للغاية (AUC 0.978) مع حساسية ونوعية عالية لمرضى الشرى، في حين كانت IL-4 ذات دقة معتدلة (AUC 0.862) مع حساسية ونوعية معتدلتين. الخلاصة: هذه الدراسة هي الأولى في محافظة ذي قار لتأكيد الدور القيم لـ TH2 في تحفيز الشرى من خلال المستويات المرتفعة من كل من IL-4 وIgE. إن الارتباط الإيجابي القوي بين هذين العاملين يشير إلى التهاب تحسسي نشط ومستمر وردود فعل فرط حساسية. كما استنتجت الدراسة أن إجمالي IgE هو علامة حيوية مثالية ودقيقة لتشخيص الشرى.

الكلمات الرئيسية: إجماليIgE ، IL-4، الشرى، Th2، الحساسية

Abstract

The IgE production and degranulation of Mast cell are significant factors in the onset and progression of urticaria, but a complex interplay of cytokines

influences its persistence . Interleukin-4 (IL-4), linked with responses of T helper 2 cell , is a crucial factor in the immunopathogenesis of urticaria. Therefore, this work highlights the role of Th2 cells in the development of urticaria by determining levels of two of their immune markers: IL-4 and IgE in Iraqi patients. Methods: Eighty-eight subjects enrolled in this work 48 of them were patients with urticarial and 40 were healthy people. A fully automated AFIAZ-10 device, and ELISA protocol used to measure total IgE antibodies and IL-4. Results :The current results illustrated higher levels of total IgE and IL-4 antibodies in patients compared to healthy controls, and a significant positive correlation (R=0.748, P<0.01) between their levels in urticaria patients. Furthermore, the ROC test results indicated that total IgE was high accurate biomarker (AUC 0.978) with high specificity and sensitivity for urticaria patients, while IL-4 had a moderate accuracy (AUC 0.862) with moderate specificity and sensitivity. Conclusion: This study is the first in ThiQar Governorate to confirm the valuable role of TH2 in triggering urticaria through elevated levels of both IL-4 and IgE. The strong positive correlation between these two factors indicates active and persistent allergic inflammation and hypersensitivity reactions. The study also concluded that total IgE is an ideal and accurate biomarker for diagnosing urticaria.

Keywords

*Total IgE ,IL-4 , Urticaria ,**Th2 , Allergy***

1. Introduction

Many people experience hives at some point in their lives, whether acute or chronic. Acute usually appears within a month and a half, while chronic hives stay for longer periods, negatively impacting patients' quality of life. The underlying causes vary, ranging from allergic reactions caused by IgE to non-allergic triggers such as physical triggers or autoimmune processes. However,

they all share the release of mediators from mast cells, which cause increased vascular permeability, vasodilation, and activation of sensory nerves [1-2] .

Polyvalent allergens bind to allergen-specific IgE antibodies on sensitized effector cells, inducing and maintaining allergic inflammation in response to the allergen. Upon interaction with the allergen, these effector cells are activated, leading to the release of potent inflammatory mediators, inflammatory cell recruitment, antigen presentation, and allergen-specific antibody responses (IgE) [3].

Cytokines play a critical role in regulating inflammatory responses and can be considered as potential biomarkers related to urticaria [4] . Among these cytokines , IL-4 stands out as a potent pleiotropic cytokine with a wide range of functions, particularly in allergic inflammation.IL-4 Primarilyregulated antibody production, inflammation, and thedifferentiation of naive T cells into effector T-cell (Th2 cells) . Given the central role of IgE-mediated mechanisms in many forms of urticaria, investigating the contribution of IL-4 is crucial [5-7].

Studies have shown elevated levels of total and specific IgE in a significant proportion of urticaria patients, particularly in chronic spontaneous urticaria (CSU) with an autoimmune component. [8-9]. IL-4, often in synergy with IL-13, upregulates the expression of CD40 ligand on T cells and CD40 on B cells, providing co-stimulatory signals necessary for IgE production. Furthermore, IL-4 promotes the expression of germline ε transcripts and subsequent recombination, facilitating the class switch to IgE. Thus, increased IL-4 expression in the urticaria patients may augment their IgE production; thus, increasing mast cell sensitization and degranulation [10-13].

It is clear from the above that elevated levels of total IgE and IL-4 reinforce a role in Th2-mediated immune responses that cause urticaria. So , this work aims to elucidate the immune responses underlying urticaria,via focusing on the

cytokine (IL-4) and immunoglobulin E (IgE) axis , and using results to improve diagnostic indicators and pave the way for targeted therapies aimed at modulating IL-4 and IgE pathways in the treatment of urticarial .

2. Patients and Methods

This work included 48 patients who visited the Dermatology and Venereology Department at Al-Nasiriya Teaching Hospital and private clinic of Al Noor Specialized Center for Dermatology between October 2024 and February 2025, Cosmetic and Laser. They were randomly selected according to eligibility criteria. Patients with autoimmune diseases or those taking immunosuppressive medications or steroids were excluded. Forty apparently healthy volunteers were included as a control category .

Five milliliters were withdrawn intravenously from all participants to obtain serum, which was stored at -20°C until analytical use. Serum total IgE levels were determined using a fully automated AFIAZ-6 fluorescence immunoassaydevice, and a sandwich ELISA protocol was used to measure IL-4 levels using the Human Interleukin-4 provided by FineTest® Company-China .

3. Statistical Analysis

"Data were analyzed using SPSS version 26. Continuous variables were presented as mean ± standard deviation, and the t-test was used to compare the means of two groups. Pearson's correlation coefficient (r) and ROC curve were used to analyze the current data. A p-value <0.05 was considered statistically significant".

4. Results:

Current data showed that 17 (35.4%) of the patient group were male, while the proportion of female patients was 31 (64.6%) and female to male ratio was

1.8:1 . Healthy individuals were equally distributed (50%) between males (20) and females (20) Figure 1 . Table 1 listed the patients

Fig 1. Distribution of patients according to sex

Also, the current resells demonstrated no significant difference in distribution of patients and healthy among age groups , but the patients and healthy were more frequent in age group (18-32) followed by (3-17) . The patients divided according to duration of disease into groups chronic aurticariapatients 29(60.4)with signs ongoing more than six week ,and acute urticariapatients 19(39.6) that appeared suddenly signs and symptoms .

Table 1. Distribution of the Patients and Healthy according to age

Age Groups	Patients	Healthy	Total
3-17	11	7	18
18-32	27	18	45
33-47	5	10	15
48-62	5	5	10
Total	48	40	88
X2	3.6585NS		
P-value	0.3		

Furthermore, the findings of total IgE and IL-4 levels were elevated in the patient group compared to healthy controls. However , the results of the patient

and control group serum samples are listed in Table 2. A significant strong positive correlation was indicated between sera totalIgE level and IL-4 levels (R= 0.78, p<0.01) , Figure 2 .

Table 2. Total IgE and IL-4 Means Levels in the Studied groups

Groups	**IL-4 mean± SD**	**Total IgE mean± SD**
Patients	623.04±286.8	315±196
Healthy	310.54±91.7	83.075±25.9
T test	5.417	7.737
P value	<0.001	<0.001

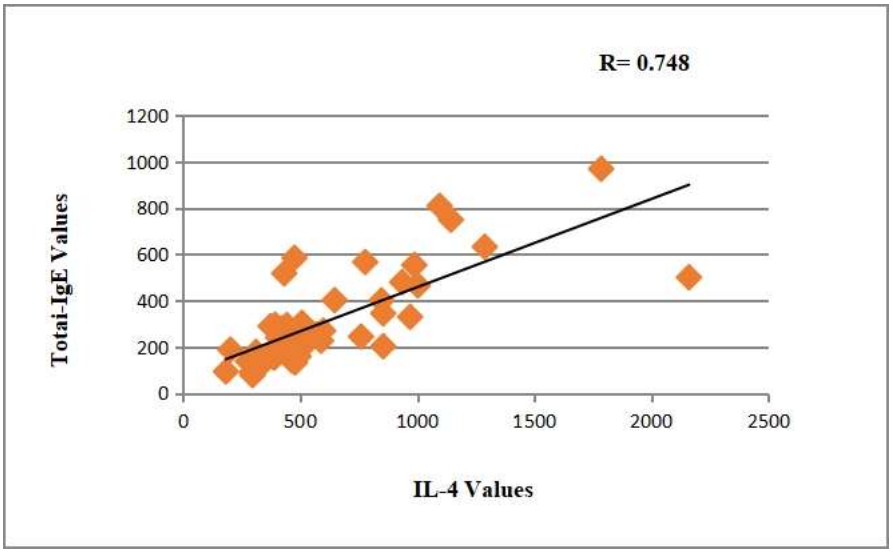


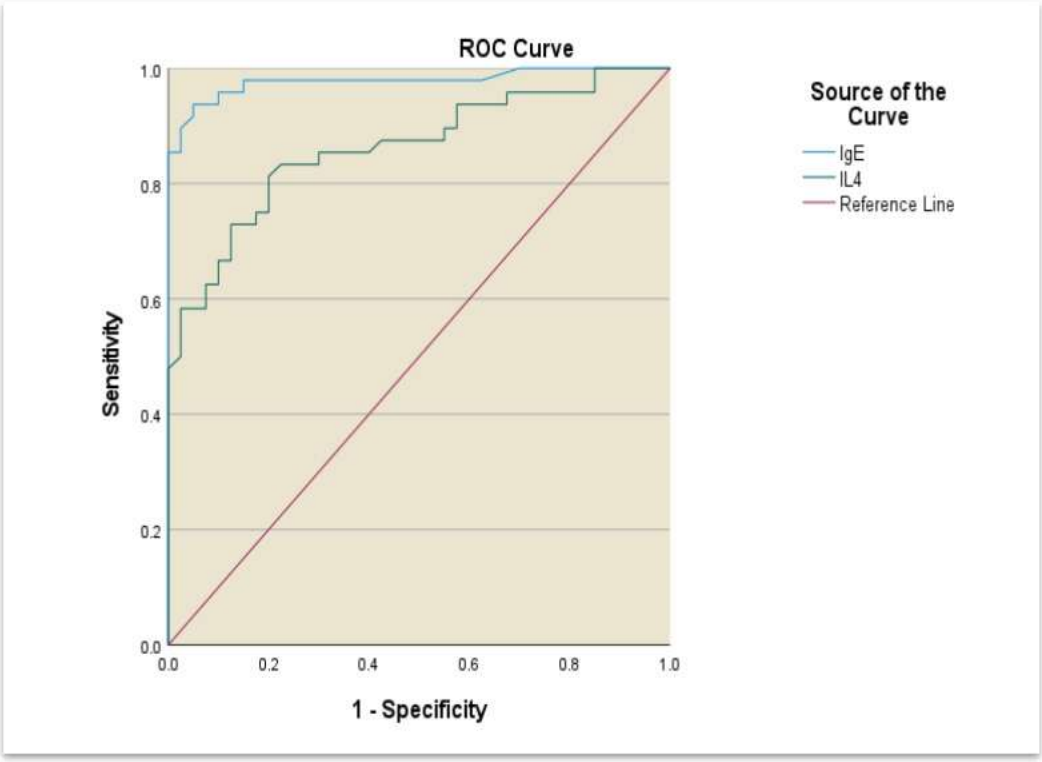
Fig 2. Correlation between IL-4 & Total IgE

According to the ROC curve, the P-values of the ROC curve were obtained for each immune parameters , Table (3) demonstrate the calculated results for tested selected variables as well as to detect the validity of both markers in diagnosing urticaria , Figure (3)

Table 3. ROC test for urticarial Patient and Healthy

Area Under the Curve					
Test Result Variables	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
IgE	0.978	0.015	.000	0.949	1.000
IL-4	0.862	0.039	.000	0.786	0.938

The result indicated that Total IgE have the most sensitive and specific values makes its the best and exellent parameters with high accracey in diagnosis urticaria disease ,while IL-4 had amoderate accuracey in diagnosis of urticaria



disease with fair sensitive and specific values.

Fig. 3.Receiver operator characteristic curve analysis of Total IgE& IL-4 for the calculation a possible diagnostic cut-off value in studied sample

5. Discussion

Two immune biomarkers in urticaria were investigated by comparing them in patients and healthy controls: total IgE and the cytokine IL-4, which are

thought to be important in the pathogenesis of the disease.The results pointed an elevated serum levels for both markers (total IgE and IL-4) with high significant in patients compare to healthy and this results were in align with previous study that indicated both of these were significantly higher in patients with popular urticaria[14]

Kessel et al. found that total serum IgE levels are frequently elevated in patients with chronic urticaria and these elevated levels linked with disease severity and duration of disease [15]

The elevated total IgE level observed in patients is due to it is mediated of type I hypersensitivity reactions,and its ability to regulate mast cell activation and stimulate the release of histamine, and other mediators, which interact with the high-affinity IgE receptor (FcRI) on cutaneous mast cells and basophils, leading to the onset of allergic reactions responsible for causing urticaria and its severity within minutes to several hours [16-17].Moreover, published data suggests that a high titer of total IgE in CSU patients due to autoreactiveIgE of a lipophilic nature [18]

On the other hand, the results also showed “a significant, strong positive correlation between IL-4 and Total IgE,” indicating a close relationship between these two immune parameters. This result was consistent with [14] , [19] . L-4 enhances the progression and differentiation of Th2 cells. It also controls lymphocyte functions, such as synthesis of IgE in B cells [10–13]. subsequently, IL-4 plays a crucial role in the pathogenesis of urticarial

According to the ROC curve, total IgE had optimal accuracy (AUC 0.978) with high sensitivity and specificity, making it the best and most distinctive criterion in diagnosing urticaria. This result was in agreement with an Iraqi study by Abdul Hussein, who found that the area under the curve was (0.960) for total IgE and characterized it as an accurate biomarker for CSU [20]. While these

results were higher than those indicated by Bader, who found that the AUC for total IgE in serum was 0.742 with moderate accuracy in diagnosing urticarial [21] .On the other hand, the results showed that IL-4 had moderate accuracy (AUC = 0.862) indicating overall good performance in diagnosing urticaria with fair sensitivity and specificity values.

6. Conclusion

It is concluded that the raised levels both IL-4 and IgE confirm a valuable role of TH2 in urticarialpromotion,and the strong liner correlation between them refers active ongoing allergic inflammation and hypersensitivity reaction.Total IgE considers also an optimal accurate biomarker for diagnosing urticaria in Iraqi patients of Thi-Qar .

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