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Assessment of Immunoglobulin-E and Interleukin-4 Levels in Papular Urticaria Patients

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Abstract

Background: **Papular urticaria is a common and often annoying disorder manifested by chronic papules caused by a hypersensitivity reaction. The link between atopic immune responses (high serum IgE, IL-4) and the development of rash is clear and has been extensively evaluated in the literature.** ***Aim:*** **This study was designed to find possible co relation between serum levels of IgE and IL-4 and popular urticaria.** ***Patient and Methods:*** **A case control study was done that included 30 patients and 30 controls who were selected randomly according to the eligibility criteria. Assessment of serum IG-E and IL-4 levels was evaluated using sandwich ELISA approach.** ***Results:*** **Twenty-six patients (87%) have borderline level of IgE, 1 (3%) have high level, while normal IgE level was found in 3 (10%). In the control group, 3 subjects (10%) have borderline level of IgE and 27 (90%) have normal level, while no subject had high IgE level were found.** ***Conclusions:*** **The present study confirmed the significantly higher values of serum IgE and IL-4 in papular urticaria patients. There was statistically significant correlation between the IL-4 and IgE levels in papularr urticaria patients.**

Key Words: Atopy, Hypersensitivity, Urticaria, Ig-E, IL-4

Introduction

Papular urticaria is a common and often annoying disorder manifested by chronic or recurrent papules caused by a hypersensitivity reaction to the bites of mosquitoes, fleas, bedbugs, and other insects(1). Papular urticaria is characterized by crops of symmetrically distributed pruritic papules and papulovesicles. Papules may occur on any body part, but they tend to be grouped on exposed areas, particularly the extensor surfaces of the extremities. Scratching may produce erosions and ulcerations. Secondary impetigo or pyoderma is common(2). Morpholog ic and immunohistochemical evidence suggest that a type I hypersensitivity reaction plays a central role in the pathogenesis of papular urticaria. The reaction is thought to be caused by a hematogenously disseminated antigen deposited by an arthropod bite in a patient who is sensitive. However, the putative antigen is unknown, this theory is supported by the fact that these lesions can and often do occur in areas away from the bites(3). The presence of immunoglobulin and complement de-

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posits in the skin of some patients with papular urticaria suggests that the lesions may be due to a cutaneous vasculitis. The deposits were most frequently seen in lesions within 24 hours of their development. The presence of granular deposits of Clq, C3, and immunoglobulin M (IgM) in superficial dermal blood vessel walls suggests that immune complexes (IgM aggregates) may be primarily involved in the pathogenesis, with complement activation initiated by Clq through the classic pathway. But a T helper shift may be present, similar to what is observed in atopy in which there is increased levels of interleukin 4 (IL-4) and immunoglobulin E (IgE)[4]. The link between atopic immune responses (high serum IgE, allergen-specific IgE, production of T-Helper 2 (Th2) cytokines such as IL-4and IL-13) and the development of asthma is clear and has been extensively evaluated in the literature[5]. In papular urticaria, skin lesions and pruritus are caused by either an allergic or nonallergic mechanism; histamine is thought to be the most important biochemical mediator in papular urticaria. It is known to cause the classic wheal-and-flare response that is observed with urticaria and with positive results on allergy skin tests. Studies have shown that histamine is present in fluid taken from urticarial wheals. Mast cells are the major histamine-releasing cells of the skin[6]. Some studies report increased numbers of mast cells in urticarial lesions. The mast cell possesses high-affinity receptors for immunoglobulin E (IgE). In allergic reactions, adjacent IgE molecules, which are bound to the surface of mast cells by the high-affinity IgE receptors, are cross-linked by allergens, leading to the release of histamine and other mediators[7]. Because of the increased IgE level in the patients with atopic diseases and it is expected to be increased in papular urticaria. This study was designed to assess both IgE and IL-4 levels in papular urticaria patients aiming to find out if there is a strong association between atopy, papular urticaria, and serum IL-4 and Ig E levels.

Patients and Methods

A Case control study was carried out in the dermatology outpatient clinic in Suez Canal University Hospital in Ismailia. 30 patients were selected randomly according to the eligibility criteria. Patient with other skin diseases, autoimmune diseases or patients receiving immunosuppressive drugs or steroids are excluded from the study. 30 healthy volunteers were selected as control group**.** All subjects were carefully evaluated by history taking and full clinical examination. An approval was taken from Suez Canal University Hospital to do the study. Informed consent was obtained from all patients or their parents before inclusion in the study. They were informed about the aim of the research and the results. Venous blood samples of all patients were collected during the patient visits to our department and the obtained serum probes were aliquoted and stored at –20°C until further analysis. Determinations of serum IgE levels were performed with a widely used, commercially available enzyme linked

immunsorbant assay (ELISA), sandwich ELISA protocol. Then Human Interleukin-4A (IL-4A) was also assessed using the ELISA Core Kit[8].

Statistical analysis

Data was collected and analyzed using SPSS program, statistical package for social sciences. Descriptive statistics (frequency, means, SD and percent) was used to describe demographic and pathophysiological correlated data. Chi square testing was used and p value of ≤0.05 was considered statistically significant and ≤ 0.01 was considered as high statistical significance. Student t–test was used to determine the statistical significance of continuous variables.

Table 1: Comparison between patients with popular urticaria and and control group according to IgE level

IgE level	Control (n=30)	Patients (n=30)	p-value
Normal (<20 IU/ml)	27	3	
Borderline (20-100 IU/ml)	3	26	0.0001
High (>100 IU/ml)	0	1	

Significant p-value at <0.05

Results

The age group of the studied patients ranged from 1- 30 years with majority (50%) of the patients between 1-5 years, while the minority (10%) of the patients from 5-10 years. A family history of atopy was positive in 18 (60%) patients and negative in 12 (40%) patients. Family history of papular urticaria was positive in 6 (20%) of study patients. The level of IgE of studied patients according to results of IgE showed 26 patients (87%) have borderline level, 1 (3%) have high level, while normal IgE level were found in 3 (10%). The level of IgE of the control group according to results of IgE was 3 subjects (10%) have borderline level and 27 (90%) have normal level, while no subject had high IgE level were found (Table 1). IgE level was significantly higher in patients compared to control (38.8±17.4 *vs.* 8.4±2.6, p=0.0001). Additionally, IL-4 level was statistically higher in patients compared to control (63.9±27.3 *vs.* 5.2±2.1, p=0.0001) (Table 2). A positive correlation was found between serum IgE level and IL-4 (r= 0.37, *p*= 0.003) (Figure 1).

Table 2: IgE andIL-4 levels in popular urticaria patients and control group

	Control (n=30)	Patients (n=30)	p-value
IgE	8.4±2.61	38.8±17.4	0.0001
IL-4	5.2±2.13	63.9±27.3	0.0001

IgE= (IU/ml); IL-4=(pg/ml)

Discussion

Papular urticaria is a common and often annoying disorder manifested by chronic or recurrent papules caused by a hypersensitivity reaction to the bites of mosquitoes, fleas, bedbugs, and other insects. Individual papules may

surrounded by a wheal and display a central punctum[1]. Papular urticaria tends to be evident during spring and summer months. Severity is often related to the host response to the salivary or contactant proteins. This eruption occurs primarily in children, but they eventually outgrow this disease, probably through desensitization after multiple arthropod exposures[2]. This condition, however, can also occur in adults, albeit at a much lower rate. Unfortunately, children affected by these eruptions are frequently misdiagnosed and often subject to expensive evaluations including invasive and unnecessary procedures[9]. In our study, age distribution of was around 60% at age between 1-10 yrs and this agrees with the results of other researchers who found that papular urticaria predominantly in children aged 0-5 yrs[10].

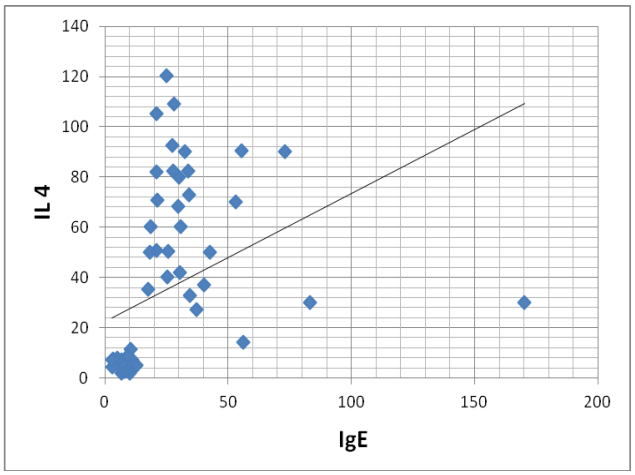

Figure 1: Scatterplot of the relation between IgE and IL-4 in papular urticaria patients (r= 0.37, P = 0.003)

In this study gender distribution of studied patients was around 57% shows that female tendancy of papular urticaria and this agree with other authors, as papular urticaria is more common in females than males[11]. In papular urticaria the presence of eosinophils, predominance of CD4-positive T cells in lesions, and IgE response suggest a Th2 immune response to flea proteins in patients with papular urticaria[12]. Atopic individuals have a persistent Th2 response accompanied by high IgE production[13]. Therefore, it is possible that papular urticaria could not be a separate entity, but really it could be considered one of the atopic marches. And this agrees with this study, as atopic background was present in 60% of patients, and 20% of patients have positive family history of papular urticaria. In this study we estimated the IgE level and we found a boarderline high level in 90% of the patients and that agrees with the results of other researchers who found an increase in IgE level in high percentage of papular urticaria

patients[10]. We also determined IL-4 level in papular urticaria patients; however there is no research addressed the same subject. In our study there was significant relation between IL-4 and papular urticaria which point to role of Th2 and IL-4 pathogenesis of papular urticaria. In this study, family history of atopic diseases (allergic rhinitis, food allergy, asthma, atopic dermatitis) and papular urticaria were significantly correlated to IL-4 and IgE high levels. This can be explained by enhanced Th2 mechanism that may be related to hereditary and genetic background. The relation between IgE and IL-4 was statistically significant in papular urticaria, so both are dependent on each other and elevated together, so we approved the role of Th2, IL-4 and IgE in etiopathogenesis of papular urticaria.

Conclusion

Both IL-4 and IgE level are significantly higher in patients with papular urticaria compared to the control group. The imbalance of IL-4 level may play a critical role in the pathogenesis of papular urticaria.

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