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Evaluation of Total Serum Immunoglobulin E in Alopecia Areata

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Abstract

Background: Alopecia areata (AA) is an autoimmune non-scarring hair loss disease, in which B cell stimulation is suggested. Immunoglobulin E (IgE) is a member of Ig family, produced by B lymphocytes. The mechanism by which IgE might interact in the pathogenesis of AA is unknown. Total serum IgE was measured in previous studies with controversial results.

Objective: to compare total serum levels of IgE between patients with different clinical forms of AA, and healthy subjects, to find out possible role of it in the etio-pathogenesis of this disease.

Methods: Total IgE was measured by Microparticle Enzyme Immunoassay (MEIA) technique in the sera of 30 patients with varying degrees of AA with exclusion of those with possible atopic disease, and in 20 controls.

Results: We found that total serum IgE was significantly elevated in 50% of patients (particularly those with localized AA) with a mean level of 29.000 Iu/mL in comparison to controls in which IgE mean level was 20.250 Iu/mL ($p < 0.05$). IgE level was also found to be significantly higher in patients with chronic lesions (more than 1 year duration), when compared to those of less than 1 year duration ($p < 0.05$).

Conclusion: Serum IgE level is a relatively sensitive investigation for AA, particularly the localized forms, irrespective of the presence of atopy. It is more elevated in patients with chronic disease denoting a shift to T helper 2- directed immune mechanisms with secondary humoral responses.

Introduction:

Alopecia areata (AA) is an unpredictable, usually patchy; none scarring hair loss condition with any hair bearing area may be affected [1]. Papadopoulos et al., 2000 classified AA according to the extent of hair loss into the following patterns: localized or patchy AA (LAA), alopecia totalis (AT) with complete loss of hair on the scalp, and alopecia universalis (AU) which is a generalized pattern of total body hair loss [2]. Although many different pathogenic causes have been proposed, the determination of the exact underlying etiology of AA is extremely problematic. Of the numerous pathogenic processes which have been proposed, immunological, environmental, psychological, and genetic factors are the most powerful explanations [3].

Immunologically, lymphocytic attack on the lower part of the anagen follicle and ectopic expression of Major Histo-compatibility Complex (MHC) class I and II molecules on the epithelium of affected hair follicles (HF), suggested that T cells and cytokines play an important role [4]. However, T helper 2 (Th2) immune response is also incriminated in the pathogenesis of AA [5,6].

IgE is a member of the Ig family of proteins produced by B cells in the spleen, lymph nodes, and locally in tissues [7]. It is now well established that the induction of IgE synthesis in human B cells requires three types of signals. The first signal is delivered through the B cell antigen receptor, the second signal is provided primarily by cytokines derived from Th2 cells, and the third signal is provided via the interaction between the constitutively expressed CD40 molecule on B-lymphocytes and CD40 ligand, expressed on activated T lymphocytes [8,9].

Unfortunately, the mechanism by which IgE might interact in the pathogenesis of AA is unknown. One of the possible explanations is supported by the immune status of AA [10]. However, Different studies have measured IgE in AA patients with controversial results [11,12,13]. Therefore, to compare total serum levels of IgE between patients with different clinical forms of AA, and healthy subjects, to find out possible role of it in the etiopathogenesis of this disease.

Methods:

Thirty patients with AA were included in the present study representing the patients group. They were collected from the Dermatology Outpatient Clinic, Ain Shams University Hospital during the period from January, 2008 till July, 2008. They were 20 males and 10 females and their age ranged from 6 to 45 years. The control group consisted of 20 ages- and sex- matched generally healthy subjects; 13 males and 7 females, with no scalp lesions in their personal history or on clinical examination. All subjects of the study (patients and controls) were subjected to: full history taking, and dermatological examination including: search for possible associations with AA such as atopic dermatitis, and vitiligo, and clinical assessment of AA lesions including: number of the lesions, site and size of the lesions, and classification according to clinical severity into: LAA, AT, and AU. All subjects of the study were subjected to: stool analysis to exclude parasitic infestation and complete blood count (CBC) to determine the number of eosinophils. Patients using topical, intra-lesional or systemic agents as steroids or immune-suppressives likely to cause re-growth in AA within the past month, patients subjected to sessions of PUVA for at least 6 months before this study, and those having other types of illness such as atopic diseases and parasitic infestation that could affect the outcome of the study, were excluded.

Both patients and controls were subjected to determination of total serum IgE level using Microparticle Enzyme Immunoassay (MEIA) technique, which is a type of enzyme-linked immunosorbent assay (ELISA). The assay was performed in a blind fashion on coded samples by an investigator who was not informed of the subject's clinical status, after the collection of all samples had been completed. In healthy, non allergic adults, reference range was up to 120 IU/ml, while normal children without allergic symptoms have a range of approximately 10 to 20% of adult value (up to 24 IU/ ml).

Statistical presentation and analysis of the present study was conducted, using SPSS V12 as follows: comparison between two variables was done using Mann-Whitney test, while comparison of more than two variables was done using Kruskal-Wallis test. If P value was > 0.05, the difference was considered statistically not significant, and if P value was < 0.05, it was considered significant. Sensitivity and specificity of serum IgE level was done with Roc-curve: Receiver Operating Characteristic curve analysis.

Results:

The study included 30 patients with AA; among them, there were 20 patients (66.6%) with LAA, 5 patients (16.6%) with AT and 5 patients (16.6%) with AU. The duration of AA ranged from 2 weeks to 9 years with a mean of 18.4 months. There were two patients (6.6%) with positive family history of AA. Five patients (16.6%) showed a relation between the onset of their disease and a preceding period of stress, while 25 (83.3%) stated no relation to stress. Total serum IgE was found to be elevated in 15 of the 30 patients (50%); 4 females (13.3%) and 11 males (36.6%). Its level ranged from 3.400 to 3000.000 IU/ml with mean level of 29.000 IU/ml. They were 13 patients (43.3%) with LAA, and 2 patients (6.7%) with AU, but no elevation of serum IgE was found in AT patients. Among patients with elevated serum total IgE, 4 patients (13.3%) were children and 11 patients (36.6%) were adults. There were 6 patients (20%) with the duration of disease less than 1 year, and 9 patients (30%) with their disease of more than 1 year duration. In the control group, levels of total serum IgE ranged from 4.800 to 183.600 IU/ml with a mean level of 20.250 IU/ml. The clinical data of both patients and controls are summarized in **table 1**.

		LAA	AT	AU	Total patients	Control group
Number of subjects		20	5	5	30	20
Sex	Male	10	5	5	20	13
	Female	10	-	-	10	7
Age (year; mean)		17.4	3.9	3.6	24.96	25.5
Duration of hair loss (month; mean)		15.4 months	6.4 months	42.2 months	18.4 months	-
Relation to stress		2	1	2	5	-
Family history		1	-	1	2	-
Previous episode		3	1	2	6	-
Serum IgE (IU/mL; median)		136.15	30.8	65.2	63.5	21.1

Table (1): Summary of clinical data of the patients and the controls:

Comparison between cases and controls revealed that there was a significant difference between both groups as regards the mean total serum IgE with P- value < 0.05 **(table 2)**.

Table (2): Comparison between patients and control as regards total serum IgE IU/ ml:

Serum IgE					
Groups		**Range**		**Median**	**Mean rank**
Patients		3.4 -	3000	63.5	29
Control		4.8 -	183.6	21.1	20.25
Mann-Whitney Test	Z	-2.079			
	P-value	0.038*			

*P is significant (significant P value < 0.05)

Insignificant difference was found in serum level of IgE between both children and adults and between males and females of the patients group as P> 0.05. Serum level of IgE was found to be significantly higher in patients with lesions more than 1 year duration when compared to those with less than 1 year duration as P< 0.05 **(table 3)**.

Serum IgE				
Duration		**Range**	**Median**	**Mean rank**
<1 year		3.4 - 587.2	47.4	12.133
>1 year		9.8 - 3000	154.3	18.867
	Z	-2.095		
Mann-Whitney Test	P-value	0.036*		

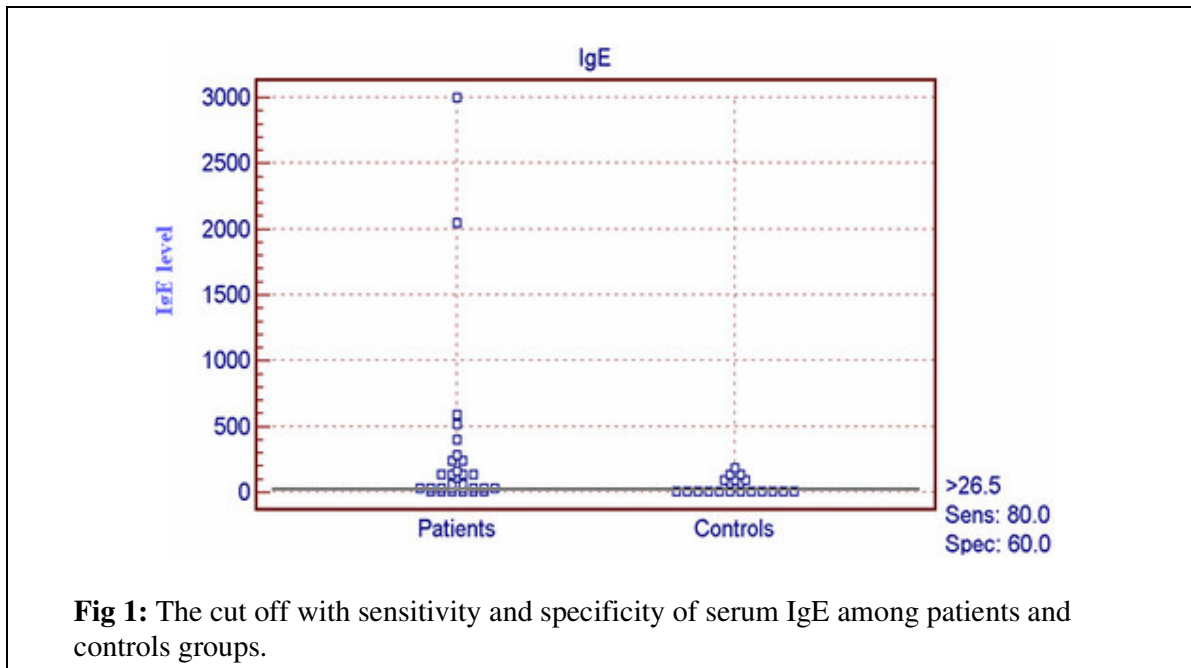*P value < 0.05 = significant

Table (3): Comparison between serum IgE in lesions with duration less and more than 1 year:

When we compared total serum IgE of patients with LAA, with AT patients, and with AU patients, a higher mean of total serum IgE among LAA was found, but this difference was not statistically significant as P> 0.05 (**table 4).**

Serum IgE				
Severity		**Range**	**Median**	**Mean rank**
LAA		3.4 - 3000	136.15	17.2
AT		8 - 112	30.8	8
AU		30.2 - 587.2	65.2	16.2
Krouskal test	Z	4.406		
	P-value	0.11		

Table (4): Comparison between serum IgE in patients with LAA, those with AT, and those with AU:

Cut off between patients and controls (>26.5) by sensitivity (80%), specificity (60%), positive predictive value (PPV) (75%) and negative predictive value (NPV) (66.7%) by accuracy (67.5%) denoted that if serum IgE level was >26.5 in a subject in our study, he was 80% a patient while if it was<26.5, he was 60% a control i.e. serum IgE is a relatively sensitive test for AA but it is non-specific (**Figure 1**).

Fig 1: The cut off with sensitivity and specificity of serum IgE among patients and controls groups.

Discussion:

In our study, we investigated total serum IgE level in AA patients with exclusion of those with possible atopic disease, to evaluate the role of immune signals for IgE induction; in AA patients, irrespective of atopic immune mechanisms. We demonstrated that the mean serum levels of total serum IgE was significantly elevated in 15 of 30 (50%) patients with LAA, AT and AU, in comparison to normal controls. Total serum IgE was proven to be 80% sensitive test in AA patients, but it was not specific (60% specificity). The association of serum IgE levels and AA has been previously investigated with varying results. O'Loughlin et al., 1977 analyzed serum IgE of 497 patients with various forms of dermatological diseases including AA, and compared their results with values from 95 normal controls. They found elevated total serum IgE in 30% of AA patients [14]. Later on, Przybilla et al., 1986 found elevated total IgE in 19.7% of AA patients [11]. Kasumagić-Halilović and Prohić 2006 also found elevated total IgE in 22 of 60 (37%) AA patients [12]. However, in contrast to these results, the total serum IgE levels were not elevated in AA patients in other previous studies [13,15]. The discrepancy between our results and the results of previous studies could be attributed to the difference in inclusion and exclusion criteria, the difference in number of patients involved, and to the different environmental factors which may affect on IgE level.

In addition to B-cell antigen receptor stimulation, Th2 cytokines, and over expression CD40 molecule [8,9], elevated serum IgE in AA patients may reflect IL-10 deficiency-associated B-cell stimulation [16], for further investigations. Another possibility to explain the elevation of total serum IgE in AA patients is the genetic mechanisms of AA, which seems to be polygenic, where several genes such as IL-4 gene [17], the gene for β subunit of type 1 IgE receptor (Fcε RIβ) [18], filaggrin gene (FLG) [19], and IL-1 receptor antagonist (IL-1 RA) gene [20] play a role in determining the disease susceptibility, and the associations of AA with atopic disease [21]. However, to our knowledge, no previous studies were done to evaluate genetic mechanisms in non-atopic AA patients with elevated serum IgE levels.

Teraki et al., 1996 found that the serum levels of IL-1α and IL-4 were significantly elevated in patients with the localized form of AA, while serum levels of IFN- γ and IL-2 were significantly elevated in patients with the extensive forms [22]. We found that total serum IgE was elevated more in LAA than in extensive forms (AT/AU). These results indicate that the immune responses are different in the localized form and the extensive forms of AA, being regulated by Th2 cytokines and Th1 cytokines, respectively. The same was suggested by Katagiri et al., 2007, who found that the levels of IFN-γ tended to increase while the levels of IL-4 tended to decrease in severe cases of alopecia [23]. Since IL-4 promotes IgE class switching, and IFN-γ have an inhibitory effect, increased levels of serum IgE in different forms of AA seem to be caused by the balance of expression of these cytokines. Further studies are needed to correlate serum levels of theses cytokines with serum IgE levels in different forms of AA.

Our study provided a correlation between the onset of AA and the level of IgE, since the longer the disease duration was the higher the level of IgE was present. Previous mouse and human data suggested that the initiation phase of AA is a heavily Th1-based immune response while, the maintenance of destruction of the HF by cytotoxic cells was suggested to be due to a shift from a Th1 response to a more chronic Th2 immune profile [24]. Thus, AA is a cell-mediated autoimmune disease with late, possibly secondary, humoral responses.

In conclusion, serum IgE level is a relatively sensitive investigation for AA, particularly the localized forms, irrespective of the presence of atopy. It may reflect the genetic and autoimmunity background of the pathogenesis of AA. Our study also provided a correlation between the onset of AA and serum level of IgE. This finding suggests a shift from a Th1 response in early AA to a more chronic Th2 immune profile, with secondary B-cell stimulation and possible IgE class switching.

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