

Study of Serum Interleukin-17 Level in Patients with Allergic Rhinitis and Nasal Polyposis

M.A.Ismael¹, K.M.Kassem¹, A.M. El Abd² and M.H.Fikry¹

¹ Professor of Otorhinolaryngology Dept., Faculty of Medicine, Benha Univ., Benha, Egypt

² Professor of Medical Biochemistry and Molecular Biology Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
E-Mail: modyhesham22.mh@gmail.com

Abstract

Rhinitis is a heterogeneous disorder characterized by one or more of the following nasal symptoms: sneezing, itching, rhinorrhea, and/or nasal congestion. Rhinitis frequently is accompanied by symptoms involving the eyes, ears, and throat, including postnasal drainage. To evaluate the expression of interleukin-17 in patients presenting with allergic rhinitis and nasal polyposis. This A case-control study was conducted on total of 60 subjects at Benha University and Benha Teaching Hospitals. They were divided into two equal groups; the cases group which included 15 allergic rhinitis case, and 15 nasal polyposis cases, and the control group which included 30 healthy subjects. All cases were subjected to complete history taking and thorough rhinological examination. In addition, serum and tissue IL-17 were measured for all cases, whereas only the serum level was measured in controls. Expression of IL-17 was significantly upregulated in NP patients and was more severe in atopic patients. In addition, there were significantly positive correlations between IL-17 and clinical and histological features. Our study suggests an important role for IL-17 in NP. Overall, we hope that present study would enable us to obtain a deeper insight into the pathogenesis of NP and provide a potential target for the treatment of NP. Based on our study results, increased IL-17 serum levels might be considered a marker of allergy severity in allergic rhinitis and nasal polyposis patients. This implies that IL-17 may be one of the etiologies in the pathogenesis of both AR and NP. Based on these results, we propose that IL-17 contribute to the development of NP and have an impact on clinical severity.

1. Introduction

There are many different causes of rhinitis in children and adults. Approximately 50% of all cases of rhinitis are caused by allergy. In the case of rhinitis caused by allergens, symptoms arise as a result of inflammation induced by a gamma globulin E (IgE)-mediated immune response to specific allergens such as pollens, molds, animal dander, and dust mites. The immune response involves the release of inflammatory mediators and the activation and recruitment of cells to the nasal mucosa [1].

Sinonasal polyposis (SNP) or chronic rhinosinusitis with nasal polyps is a chronic inflammatory pathology of the nasal and paranasal cavities [2], which affects from 1% to 4% of the population and has a clear association with asthma, aspirin sensitivity and cystic fibrosis [3].

Patients with SNP typically present with nasal obstruction, rhinorrhea, hyposmia and reduced quality of life [4]. Although polyps seem to be a manifestation of the chronic inflammation of nasal /paranasal sinus mucosa in both allergic and non-allergic subjects, the pathogenesis of nasal polyposis remains unknown, but it is probably multifactorial disease with several different etiological factors [5].

Upon exposure to an allergen – atopic individual respond by producing allergen specific IgE, which bind to IgE receptor on the mast cell of the respiratory mucosa. On re-exposure to the same allergen IgE bridged on the cell surface by allergen resulting in activation of mast cell and release granules

associated chemical mediators, which cause the symptoms of (AR) [6].

For more than two decades, immunologists have been using the Th1/Th2 paradigm to explain most of the phenomena related to adaptive immunity. The Th17 cells, was recently described as a distinct lineage that does not share developmental pathways with either Th1 or Th2 cells. Shen et al. suggested that the imbalance of Treg/Th17 may play an important role in the development of SNP and that atopy may aggravate SNP [7]. Shen et al., on another study, suggested an important part of IL-17A in SNP, and demonstrated that expression of IL-17A was significantly upregulated in SNP patients and was more severe in atopic SNP [8].

Aim of the Work

The aim of this study was to evaluate the expression of interleukin-17 in patients presenting with allergic rhinitis and nasal polyposis.

2. Subjects and methods

This A case-control study was conducted on 30 patients suffering from allergic rhinitis and nasal polyposis (Group A) and 30 apparently healthy individuals of matched age and sex as a control group (Group B). Patients were recruited from the outpatient clinic of Otorhinolaryngology Department, Benha University Hospital and Benha Teaching Hospital.

The study was approved by the local ethic committee of Benha Faculty of Medicine. An Informed consent was obtained from each individual before sample collection.

The study included patients having sneezing, rhinorrhea, nasal obstruction, irritability and fatigue, attack accompanied by itching of the nose, eyes and cough, attacks relieved spontaneously or with antihistaminic therapy.

While patients with ages more than 40 years or less than 15 years, any patient use systemic corticosteroid for a long period in order not to affect interleukin 17 serum level, patients suffering from rhinitis due to other cause than allergy and patients suffering from any systemic disorder as hypertension and diabetes mellitus were excluded from the study .

Methods

All patients were subjected to the followings

Full history taking: Personal history : Name, age, sex, occupation, residence, special habits of medical importance, marital status. Present history: Onset, course, duration of nasal symptoms as nasal obstruction, nasal discharge and sneezing. Family history of allergic rhinitis. Past history of medications (type, dose and duration), operations and general diseases. Clinical examination: Full general examination to exclude other inflammatory and systemic diseases. Detailed rhinological examination; inspection, palpation, anterior rhinoscopy, posterior rhinoscopy and nasal endoscopy. Laboratory investigations: All studied subjects were tested for: Serum and tissue level of Interleukin 17.

Assay principle

The kit was provided by a microtiter plate which has been pre-coated with an antibody specific to target antigen. Then standards and serum samples were added to appropriate microtiter plate wells with a biotin-conjugated antibody preparation specific to target antigen and then avidin conjugated to Horse Radish Peroxidase (HRP) is added to each microplate well and incubated . Then a TMB (3, 3', 5, 5'-Tetramethylbenzidine) substrate solution was added to each well . Only those wells that contain target antigen, biotin-conjugated antibody and enzyme - conjugated avidin exhibit change in color. The reaction

was terminated by adding sulphuric acid (H_2SO_4) solution and the color change was measured spectrophotometrically at a wave length $450\text{ nm} \pm 2\text{nm}$ according to the manufacturer's protocol.

The concentration of IL17 was directly proportional to the color intensity of the tested sample. The concentration of IL 17 in the samples was then determined by comparing the optical density (O.D.) of the samples to the plotted standard curve .

Statistical analysis

The clinical data were recorded on a report form . These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 20 to obtain : Descriptive data : Descriptive statistics were calculated for the data in the form of : Mean and standard deviation ($\pm SD$) for quantitative data . Frequency and distribution for qualitative data . Analytical statistics :

In the statistical comparison between the different groups , the significance of difference was tested using one of the following tests :- Student's *t*-test and Mann-Whitney test:- Used to compare mean of two groups of quantitative data of parametric and non-parametric respectively . 2- ANOVA test (F value) and kruskal -wallis test:-Used to compare mean of more than two groups of quantitative data of parametric and non-parametric respectively . 3- Inter -group comparison of categorical data was performed by using chi square test (X^2 -value) and fisher exact test (FET). Probability P value < 0.05 was considered significant.

3. Results

Age

In this study there was no significant difference (P.0.054 as measured by T test) in age between case and control groups the average age of the patients 20.2 years and ranged from 15 to 40 years. The average age of control group was 22.08 years and ranged from 15 to 40 years.

Table (1) Age distribution.

		Cases group (n= 30)	Control group (n= 30)	Statistical test	p value
Age	Mean \pm SD	20.2 \pm 4.44	22.08 \pm 4.12	t= 1.96	0.054

Gender

Our study underwent on 12 females (40%) and 18 males (60%) included as cases group.

11 females (36.6%) and 19 males (63.3%) included as control group.

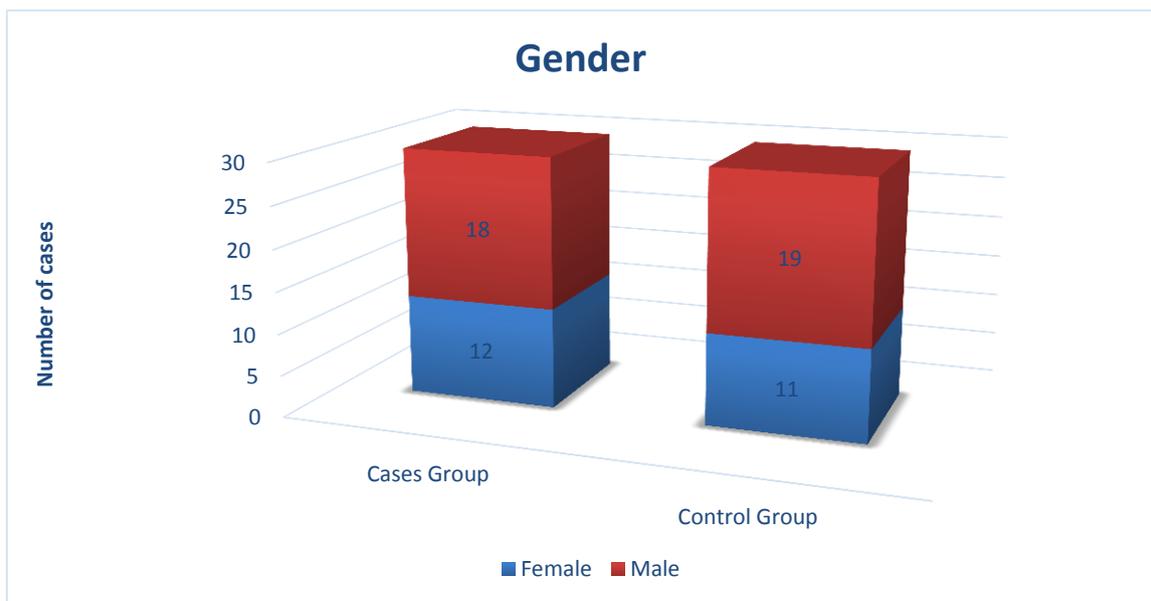


Fig (1) Gender distribution

Clinical Data of the studied patients

Clinical assessment of studied patients revealed that;21 (70%) patients had gradual onset, 27 (90%) patients had progressive course of AR and NP. Mean disease duration was 3.14years. Regarding history of

previous treatment;30(100%) patients had previous treatment for AR and NP. 15(50%) patients were giving positive family history of AR and NP as shown in table

Table (2) Clinical Data of the studied patients.

Variable		n=30	%
Onset	Sudden	9	30
	Gradual	21	70
Course	Progressive	27	90
	Stationary	3	10
Duration (years)	Mean±SD	3.14±3.66	
History of previous treatment	Positive	30	100
	Negative	0	0
Family history	Positive	15	50
	Negative	15	50

Laboratory investigations

On comparison of IL17 level between patients including AR and NP and control groups, there was a statistically significant increase in IL17 level in AR and NP patients than controls as shown in table.

Table (3) Mean ± SD & p values of serum & Tissue of IL-17 in nasal polyposis group and allergic rhinitis group compared with control group.

Biochemical parameters	Control		Cases		
			NP		AR
	Serum	Serum	Tissue	Serum	Tissue
IL-17 level	2.6599 ± 1.1027	3.363 ± 0.8249	2.584 ± 1.0618	2.9085 ± 1.030	2.093 ± 1.0361
		P:<0.05		P<0.05	P1<0.05
				P1 <0.05	

4. Discussion

There are several studies in the literature describing the relationship between AR and

cytokines . It is known that AR is a Th2-dominant disease and there are many studies exhibiting the

relationship of cytokines with AR such as Th2-based IL-4 and IL-13 [9].

Polyposis is an end disorder of mucosa that stems from various inflammations in the nasal cavity, such as nasal allergy, chronic sinusitis and aspirin-exacerbated respiratory disease. The pathogenesis is not yet fully understood. Published data indicate that AR is involved in the pathogenesis of nasal polyposis [10].

However, not all patients with AR have polyposis, or vice versa. Recent studies indicate that there is a sub population of T cells in peripheral blood and lymphoid tissue that expresses IL-17 [11].

Our data are in line with these pioneer studies by providing evidence that a subset of T cells in the nasal mucosa expresses IL-17. Whether this T cell subset plays a role in the pathogenesis of nasal polyposis needs further investigation. However, we found that IL-17+ T cells had a close relation with the specific pathogenic condition of both AR and NP, but not in patients with AR alone. This implies that IL-17+ T cells may be one of the etiologies in the pathogenesis of both AR and NP. Previous studies also indicate that IL-17 plays a critical role in nasal polyposis [12].

Data for IL-17 mediated allergic rhinitis in humans are quite limited compared to murine experimental models. Moreover, recent studies have been demonstrated that cytokine setting inducing Th 17 differentiation in humans and mice is different [13].

Wang and Liu stated the role of IL -17 producing cells in allergic reactions as "largely unclear". In 2010 for the first time IL-17 have been found to play a causative role in airway remodeling in asthmatic mouse mode. But the idea on participation of IL -17 in upper airway tissue remodeling is not clear and is still controversial [14].

IL -17 is an important effector of Th17 cells with a strong pro-inflammatory role in rheumatoid arthritis. Increased expression of IL-17 has been observed in multiple sclerosis, asthma, systemic lupus erythematosus and transplant rejection. IL-17 may play a pathogenic role in an established AR mouse model [15,16].

Expression of IL-17 is significantly higher in the peripheral blood of AR patients than in the control group [17]. Studies in recent years have shown that $\gamma\delta$ T-cells are an important source of IL-17 production [18].

Th17 cells are newly emerging Th cell subsets that link the immune response to tissue inflammation. IL-17A and IL-22 are the predominant prototype cytokines [19]. Although the main function of Th17 cells is supposed to be induction of protection against potentially harmful fungi and extracellular bacteria, a large battery of experiments with IL-17 neutralizing antibodies [20], as well as relatively high

levels of IL-17 A, showed the potential role of Th17 cells in the pathogenesis of nasal diseases [21].

For example, Wang et al. showed IL-17 antagonism significantly attenuated Th2 responses and infiltration of neutrophil and eosinophil in AR mouse model [16]. Quan et al. also reported that IL-17A-deficient mice showed a significant decrease in allergic symptoms, serum IgE levels, and eosinophil infiltration; decreased histamine and cysteinyl leukotriene release; and significantly lowered degranulation and secretion of TNF- α in marrow-derived mast cells [15]. These findings together showed the potential role of anti-Th17 cells in the management of allergic rhinitis.

A recent study on IgE production in human B cells found that IL-17 could induce B cells switching to IgE which implies Th17 involvement in the atopic phenomenon [14]. The role of IL-17 producing cells as the subject of research in the field of allergic sensitization is essential not only for increasing our understanding of the AR mechanism [22].

This study was conducted at Benha University and Benha Teaching Hospitals aiming to evaluate the expression of interleukin-17 in patients presenting with allergic rhinitis and nasal polyposis.

We included a total of 60 subjects who were divided into two equal groups; the cases group which included 15 allergic rhinitis case, and 15 nasal polyposis cases, and the control group which included 30 healthy subjects. The mean age of cases and controls was 20.2 and 22.08 years respectively. No statistically significant difference was detected between the two groups ($p > 0.05$).

Another study handling the same perspective also included 96 subjects who were divided into two groups; the cases group which included 65 allergic rhinitis patients, and the control group which included 31 healthy subjects. Like our study, no significant difference was detected between the two groups regarding patient age [9].

In the current study, the cases group included 18 males (60%) and 12 females (40%), whereas the control group included 19 males (63.3%) and 11 females (36.6%). No significant difference was found between the two groups regarding gender.

In another study, authors included 14 males and 8 females in the control group, while the cases group included 26 males and 10 females. Like our study results, no significant difference was detected between the two groups regarding gender ($p > 0.05$) [23].

In this study, the mean duration of the disease in the case group was 3.14 years (SD 3.66).

Another study reported that the mean duration of the disease was 6.78 years in the cases group [9].

In our study, serum IL-17 levels were significantly higher in patients serum compared to controls ($p < 0.05$). In allergic rhinitis cases, the mean value of serum IL-17 was 2.908, while it was 3.36 for the nasal polyposis group. However, tissue levels of

that biomarker were lower than the serum levels in the included controls. Moreover, tissue IL-17 was significantly higher in the polyposis cases when compared to allergic rhinitis group ($p = 0.03$).

These results suggest that Th17 cell may be involve in AR pathogenesis and that T-cells may have an immunomodulatory function on Th17 cells in the peripheral blood of AR patients .

Our data demonstrated increased expression of IL-17 in AR and NP patients than control group and there was increase in level of IL-17 in NP than AR patients , suggesting that IL-17 may play an important role in the development of NP .

Another study reported that serum levels of IL-17 were significantly higher in the allergic rhinitis cases compared to controls (0.68 vs. 0.45 – $p = 0.038$) [9] This agrees with our study results.

In many studies of literature , serum IL-17 and IL-22 levels of AR patients are higher than those of control groups which is similar to our study [18,22,23,24].

In the study of Ciprandi and colleagues , serum IL -17 levels of AR patients were detected higher than those of controls and also, a positive correlation was indicated between serum IL-17 level and symptom severity [25].

In another study , it was shown that serum IL -17 level in AR patients was higher while TGF- β level was lower than that in controls [26].

Another study reported that serum IL-17 levels in the AR and control groups were (668.55 ± 45.15 pg/ml) and (573.53 ± 17.42 pg/ml), respectively. The IL-17 level in the AR group was significantly higher than that in the control group ($p < 0.0001$) [18].

Tang and his associates also stated that d IL -22 and IL-17A Th cells, as well as serum levels of IL-22 and IL-17A, were significantly increased in AR patients. Moreover , they provided the first evidence that IL-22 Th cells, in addition to IL-17A Th cells, were associated with the clinical severity of AR patients [23].

Another study reported that average percentages of IL-17 producing T cells determined with flow cytometer were between 0.57 to 1.84% in healthy subjects and 1.34 to 6.84% in the patients . The mean values of IL-17 were significantly higher in patients (5.10 ± 4.40) pg/ml as compared to asymptomatic subjects (3.46 ± 1.28) pg/ml , ($p = 0.04$) [22].

Regarding the local expression of IL-17, Ba et al. showed that the number of IL-17 cells in tissues of AR patients was higher than that of controls ($p < 0.05$). They also showed that the eosinophilic cell count correlated with the number of IL-17 cells ($p < 0.05$) [26].

Interestingly , in a different report , the same authors described that the expression of IL -17 was only apparent in the nasal mucosa of patients with AR [27].

Liu et al. reported that there were no significant differences between AR and nonallergic rhinitis patients in the protein expression of IL -17 in inferior turbinate tissues [28].

Local IL-17 expression in the sinonasal mucosa is known to have ethnic and/or regional differences ⁽²⁹⁾. Another study by Katoto-michelakis et al. strengthens the importance of studies in the Asian population because there is a difference in cytokine profile in European populations that changes over time [30].

A more recent study has demonstrated that Anti -IL-17 Abs markedly reduced the number of nasal rubbing motions and sneezes , decreased eosinophil and neutrophil infiltration , reduced Th2 and Th17 responses, and increased the Treg response [31].

It is thought that future studies to be conducted relating to this subject will form new targets in treatment.

5. Conclusion

Based on our study results , increased IL-17 serum levels might be considered a marker of allergy severity in allergic rhinitis and nasal polyposis patients .

This implies that IL-17 may be one of the etiologies in the pathogenesis of both AR and NP.

Based on these results , we propose that IL-17 contribute to the development of NP and have an impact on clinical severity.

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