International Journal of Medical Laboratory 2017;4(2): 101-110.

International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Original Article

Th17 Lymphocytes Percentage in Peripheral Blood of Iranian Patients with Autosomal Recessive Hyper IgE Syndrome

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ABSTRACT

Article history
Received 19 Apr 2017
Accepted 24 May 2017
Available online 21 Jun 2017

Key words
AR-HIES
Hyper IgE Syndrome
Th17

Background and Aims: Patients with Hyper-IgE syndrome suffer from fungal and bacterial infections, especially Candida albicans and Staphylococcus aureus. Due to the important role of T helper17 (Th17) lymphocytes in defense against fungal infections, the percentage of Th17 lymphocytes was studied in the patients with autosomal recessive hyper-IgE syndrome (AR-HIES).

Materials and Methods: In this case-control study, six patients with AR-HIES (with DOCK-8 mutation) and seven healthy age and sex-matched controls were included. Peripheral blood mononuclear cells were isolated from their venous blood and the percentage of Th17 lymphocytes were determined by flow cytometry.

Results: There was no statistical difference between the percentage of Th17 lymphocytes (p=0.15) in the case and control groups. Also in comparison to the control subjects, the numbers of eosinophils were dramatically increased (p=0.000). Also, there was a significant negative correlation between serum IgE levels and Th17 lymphocytes' percentage (r=-0.927, p=0.006) and a significant positive correlation between eosinophils number and Th17 lymphocytes' percentage (r=0.557, p=0.01). Serum IgE levels showed a significant positive correlation with the numbers of eosinophils in the patients' peripheral blood with AR-HIES (r=0.961, p=0.003).

Conclusions: The numbers of Th17 in the patients with AR-HIES may not show statistical differences between the cases and controls. The numbers of eosinophils significantly increased in the patients AR-HIES compare to the controls.

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Introduction

Hyper IgE Syndrome (HIES) was first identified by Davis et. al in two red-haired girls with recurrent sino-pulmonary infections, severe dermatitis and cold abscesses [1]. This syndrome is a primary immunodeficiency disease (PID) and has been described in two major forms with autosomal recessive (AR) and autosomal dominant (AD) inheritances [2, 3].

The patients with AD Hyper IgE Syndrome (AD-HIES) are characterized by highly elevated serum IgE, facial and skeletal abnormalities, recurrent pneumonia, newborn rashes, and dental abnormalities. Most cases of HIES (about 70-90%) are categorized in this group, which are due to mutations in signal transducer and activator of transcription 3"STAT-3" [4]. Mutations in STAT-3 gene can cause impairment in Th17 differentiation and function [5, 6].

Patients with the autosomal recessive form of Hyper IgE Syndrome (AR-HIES) are characterized by elevated serum IgE levels (same as AD-HIES), blood eosinophilia, neurological disorders (which may cause death in childhood), atopy and viral infections, especially with cytomegalovirus and herpes simplex viruses. Patients with AR-HIES lack facial and dental abnormalities, which have been described in AD-HIES [1, 4, 7, 8]. Patients with AR-HIES were diagnosed with various IgE mediated allergic diseases includes asthma and food allergies. Mutations in the gene called dedicator of cytokinesis 8 protein "DOCK-8"is associated with AR-HIES. DOCK-8 gene is located on the 9th chromosome in p24 location and consists of 47 exons and its length is nearly 190 kbps [9, 10]. DOCK-8 belongs to DOCK family, which plays an important role in lymphocytes migration, morphology, adhesion and growth [10, 11]. Mutations in DOCK-8 lead to impairment in $CD4^+$ and $CD8^+$ lymphocytes proliferation. As DOCK-8 plays an important role in lymphocyte function and activation of T lymphocytes, mutations in DOCK-8 cause malfunction in lymphocytes and leads to AR-HIES [12, 13].

T helper 17 (Th17) lymphocytes are T helper $CD4^+$ lymphocytes that produce Interleukin (IL)-17 family cytokines [14, 15]. They play an important role in inflammation, autoimmunity, neutrophil maturation and chemotaxis and defense against bacterial and fungal infections [16-18]. In patients with AD-HIES (with mutations in STAT-3), Th17 impairment leads to increased susceptibility to fungal and bacterial infection [19].

The rate of consanguineous marriages in Iran (about 38.6%) is relatively high comparing most countries worldwide. Among PID patients this rate is even higher (up to 65.6%) [20]. Because of the inheritance pattern of many PIDs like HIES (autosomal recessive) and high rate of consanguineous marriages in Iran, the prevalence of these diseases is higher than the expected prevalence. As in the patients with AR-HIES there is an impairment in DOCK-8 gene and this is responsible for autosomal recessive form of HIES, impairment in Th17 lymphocytes functions and also some related

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forms of IgE dependent allergies and asthma,so this study was designed to determine the percentage of Th17 lymphocytes in peripheral blood of patients with AR-HIES compared to healthy controls.

Materials and Methods

Subjects

Six children diagnosed with AR-HIES (three girls and three boys based on the patients' clinical presentation and immunological and genetic studies) were enrolled in a case-control study. The numbers of selected patients were under observation of statistics consultant and also based on previous studies accomplished. All patients were referred to referral hospitals in Tehran from 2014 to 2016. Informed contest was obtained from all parents or legal guardians of the studied group as well as controls. Seven unrelated healthy aged-sex matched children (three girls and four boys) were also included as a control group. Five milliliters of venous blood were obtained from each subject. This research was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences.

Isolation of peripheral blood mononuclear cells (PBMCs) and lymphocytes culture

PBMCs were isolated from the whole venous blood via Ficoll 1.077 (Biowest, Austria) gradient centrifugation. In order to separate monocytes, 4×10^6 PBMCs were incubated for 3 hours in Roswell Park Memorial Institute medium (RPMI) 1640 (Gibco, USA) with 10% fetal bovine serum (FBS) (Gibco, USA) in a cell culture flask. Monocytes were adhering to flask wall and the supernatant was collected. Lymphocytes were cultured overnight in RPMI 1640 containing10% FBS, 100 IU/ml Penicillin, 100 IU/ml Streptomycin and L-Glutamin, and stimulated with 40 ng/ml phorbol 12-myristate 13-acetate (Sigma-Aldrich, St. Louis, MO, USA), 10^{-5} M Ionomycin (Sigma-Aldrich, St. Louis, MO, USA) and 1 µg/ml Golgi Plug (BD biosciences, USA) in a CO2 incubator at 37°C.

Flow cytometry assay

After overnight culture, lymphocytes were stained with anti-CD3-PECy5 (BD Biosciences, USA) and anti-IgG1κ PECY5 as its isotype control (BD Biosciences, USA). For intracellular staining, the lymphocytes were fixed and permeabilized using BD Cytofix/Cytoperm ™ (BD Biosciences, USA), then stained with anti-IL-17A-PE (BD Biosciences, USA) and anti- IgG1κ-PE (BD Biosciences, USA) as isotype control, in different tubes. Finally, the results were assessed by a BD FACS Calibur flowcytometer and Quest Pro software version 4.02 (BD Biosciences). Flow cytometry data were analyzed by FlowJo software, version 7.6.1.

IgE measurement

Serum IgE levels were measured using the IgE Human enzyme-linked immunosorbent assay (ELISA) Kit (Abcam, USA). When the procedure of test was performed completely according to test protocol, stop solution added and the samples read at 450 nm with a microtiter plate reader within 15 minutes. Results are reported as Iu/ml of IgE.

Eosinophil count

The numbers of eosinophils were investigated using peripheral blood smear in both case and control subjects.

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Statistical analysis

The Shapiro-Wilk test was applied to test normality of the data. Comparison between two-groups in parametric data was performed by one sample T test and for nonparametric data Mann-Whitney U test was applied. The correlations between different parameters were assessed by Pearson's correlation test. P values less than 0.05 were considered to be significant. All data analyses were performed by IBM SPSS Statistics version 16 (International Business Machines Corp., Armonk, NY, USA) & GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

In this case –control study, 6 patients with AR-HIES and 7 age-sex matched healthy controls were included. The mean±SD of the age were 9.62±5.82 years in case group and 9.17±4.06 years in the control group and there was no significant difference between ages in case and control groups (p=0.89).

Clinical manifestations of patients with AR-HIES

Table 1 shows demographic information of patients with AR-HIES. All patients were Iranian and born from consanguineous marriages. The mean of SCORAD index was 65.03.

Table 1. Demographic information of patients with AR-HIES

No.	Age (yr)	Sex	SCORAD	Upper respiratory infections	Lower respiratory infections	Bacterial and fungan infections	Atopy status	Skeletal and face characteristics	Virtual infections	Serum IgE (Iu/ml)	Eosinophil count (/µl)
1	12.3	M	65.5	Sinustis	Pneumonia>5 times	Candidiasis	Eczema	Retained primary teeth	Cytomegalo virus	31500	1344
2	6.6	F	61.8	Otitis	Pneumonia>3 times	Candidiasis	Eczema	None	HSV	14900	2785
3	5.7	F	63.2	-	-	*S. Aureus* Candidiasis	Newborn rashes, Eczema, Food allergy	None	-	21800	5214
4	19.2	F	58.7	-	-	Candidiasis	Newborn Rashes	None	-	8000	2029
5	10.4	M	69.1	Sinustis, Otitis	Pneumonia>5 times	*S. Aureus* Candidiasis	Generalized rashes, eczema	Deep Set Eyes	HSV	2478	2890
6	2.5	|M	71.9	-	-	S. Aureus	Eczema, Food allergy	Increased Nasal Width	-	5460	1410

HSV = Herpes Simplex Virus *; S. Aureus=Staphylococcus aureus*; F= Female; M= Male

Th17 lymphocytes

The mean ± SD of percentage of Th17 lymphocytes in the case and control groups were 3.63±1.01 and 4.33±0.65, respectively (Fig. 1) and the mean numbers of Th17 lymphocytes in PBMCs of cases and healthy subjects were 109.5 cells/ml and 105.3 cells/ml, respectively. This difference was not statically significant (p=0.15).

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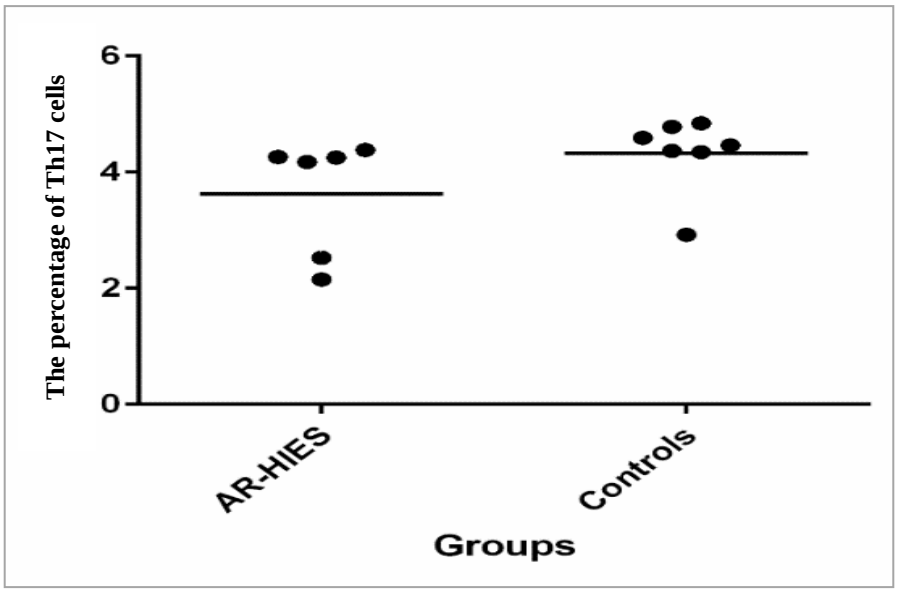


Fig. 1. The percentage of Th17 lymphocytes in patients with AR-HIES compared to healthy subjects

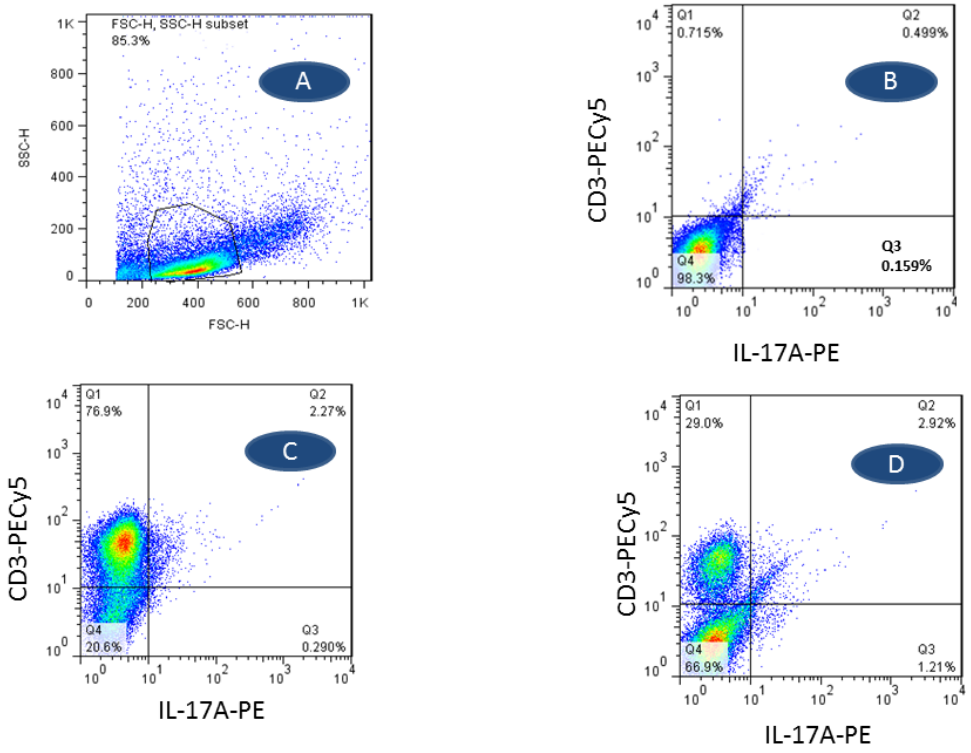


Fig. 2. Flowcytometry diagrams in healthy subjects and the patients with AR-HIES A: Forward scatter to side scatter, B: Isotype control for CD3-PECy5 and IL-17A-PE, C: the percentage of Th17 lymphocytes in healthy subjects, D: the percentage of Th17 lymphocytes in patients with AR-HIES

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Eosinophils

As shown in Fig 3, the mean of eosinophils absolute count in patients with AR-HIES were 2612 cell/µl, which was highly elevated compared to control group (162.8 cell/µl) (p=0.000).

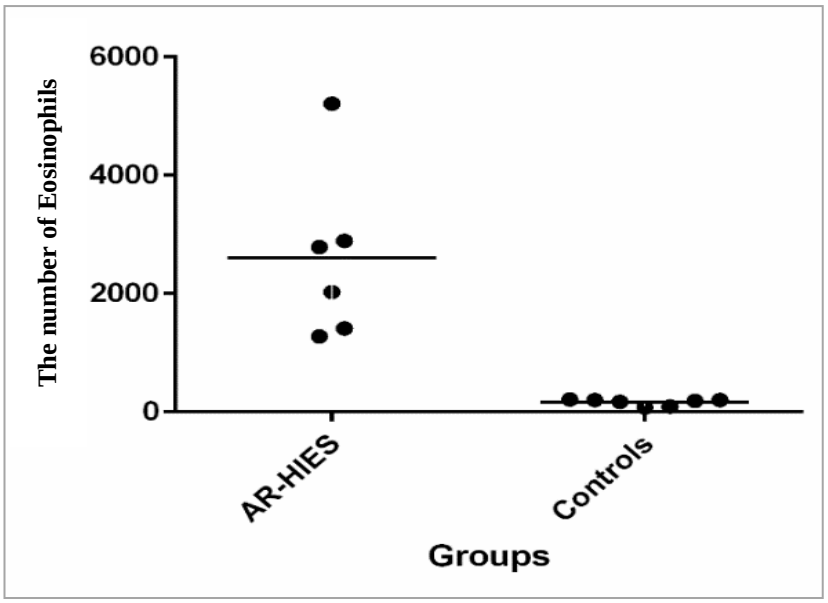


Fig. 3. The numbers of Eosinophils in patients with AR-HIES compared to healthy subjects

Serum levels of IgE in patients with AR-HIES

The mean±SD of IgE in patients with AR-HIES was 14023±9420 Iu/ml. Because parents of children in the control group did not sign contest for this section of the study we were unable to compare serum IgE levels in both groups, although serum IgE levels in patients were obviously higher than normal ranges in reference books.

Correlation assessment

In our study, among the patients with AR-HIES, there was a significant negative correlation between serum IgE levels and Th17 lymphocytes percentage (r=-0.927, p=0.006) and a significant positive correlation between eosinophils number and Th17 lymphocytes percentage (r=0.557, p=0.01). Serum IgE levels showed a significant positive correlation with the numbers of eosinophils in peripheral blood of patients with AR-HIES (r=0.961, p=0.003). Also, in our study, a negative correlation was shown between serum IgE levels and Th17 lymphocytes in the patients with AR-HIES (r=-0.9, p=0.004).

Discussion

Hyper IgE Syndrome is a primary immunodeficiency disease, characterized by increased serum IgE, eosinophilia, recurrent pneumonia, susceptibility to fungal and bacterial infections, including *candida albicans* and staphylococcus *aureus* and also viral infections like Cytomegalovirus (CMV) and herpes simplex virus (HSV) in patients with AR-HIES [21]. Due to high prevalence of consanguineous marriages in Iran, which

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consists about one third of all marriages, the rate of inherited diseases, including PIDs are higher compared to the other countries [20]. Considering the important role of Th17 lymphocytes in defense against fungal infections, this study was designed to compare the percentage of Th17 lymphocytes in the patients with AR-HIES and healthy controls.

According to the results of the present study, the percentage of Th17 lymphocytes in patients with AR-HIES is similar to the healthy controls. So, the reduction of Th17 lymphocyte population is not the reason of increased susceptibility of these patients to fungal infections.

Th17 lymphocytes are known as an important mediator in inflammatory responses and they have a key role in defense against pathogens in mucosal and epithelial surfaces. One of the most important roles of these lymphocytes is a defense against bacterial and fungal infections, including candida albicans and staphylococcus aureus [22]. Some studies have shown that decreased Th17 lymphocyte population increases the susceptibility to such infections [23, 24]. There are controversial results about the Th17 lymphocyte population in the patients with AR-HIES. Our results showed that there is no significant difference between the percentage of Th17 lymphocytes in the patients with AR-HIES and the controls (p=0.15). Boos et. al has reported the same results because they used the same technique (flow cytometry) and the same numbers of patients with AR-HIES [25]. However, Engelhardt et. al found a significant decrease in Th17 lymphocytes population, [26]. They suggested that this reduction in Th17 lymphocytes, may be due to the role of DOCK-8 gene in the regulation of lymphocytes organization, and mutation in DOCK-8 may impair Th17 differentiation and function. This conflict in the results of our study and Engelhardt et. al may be due to the numbers of studied patients and also the technique used to investigate the numbers of Th17 lymphocytes, which they manipulated polymerase chain reaction to detect impairment in Th17 lymphocytes. On the other hand, in a study of Th17 cells flow cytometry seems to be a better technique compared to PCR to detect Th17 lymphocytes and each mRNA expression in PCR does not necessarily indicatethe presence of Th17 lymphocytes.

One of the laboratory manifestations of HIES is blood eosinophilia [25, 27]. As predicted, the number of eosinophils was much higher in the patients with AR-HIES included in this studycomparing to the healthy controls.

Our results showed that there is a significant correlation between the number of eosinophils and Th17 lymphocytes in the patients with AR-HIES. This may due to this fact that eosinophils express IL-17A and IL-17F receptors constantly and IL-17 production by Th-17 lymphocytes affects eosinophils [28, 29]. Also, Phyllis et. al showed that in the patients with asthma there is a correlation between Th17 lymphocytes and Eosinophils, so that human eosinophils were found to constitutively express receptors for IL-17A, IL-17F, and IL-23 at the protein level. IL-17A, IL-17F, and IL-23 could induce the release of chemokines GRO-α/CXCL1, IL-8/CXCL8,

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and MIP-1β/CCL4 from eosinophils, while IL-17F and IL-23 could also increase the production of proinflammatory cytokines IL-1β and IL-6. Synergistic effects were observed in the combined treatment of IL-17F and IL-23 on the release of proinflammatory cytokines, and the effects were dose-dependently enhanced by IL-23, but not IL-17F. Further investigations showed that IL-17A, IL-17F, and IL-23 differentially activated the ERK, p38 MAPK, and NF-κB pathways. So, there is a positive correlation between Th17 lymphocytes and eosinophils [30].

In this study, the numbers of Th17 lymphocytes and serum IgE levels in the patients with AR-HIES showed a significant negative correlation. In a study, which performed by Miossec, the results were in consistent with our findings, which may due to the role of Th17 lymphocytes in suppression of Th2 lymphocytes and subsequently reduced serum IgE levels. As in the patients with AD-HIES the numbers of Th17 lymphocytes dramatically decreased, the balance between Th17/Th2 lymphocytes goes ahead towards Th2 lymphocytes and IgE production [31].

In our study, there were some limitations, including the lack of the atients' cooperation, delay in receiving materials and antibodies from companies. Also, there was not a FACS Calibur flow cytometer to evaluate the numbers of Th17 lymphocytes, so the samples should be referred to the general laboratory of Shahid Beheshti University of Tehran.

Finally, as in some studies they showed that the serum levels of interferon gamma reduced in the patients compared to the healthy subjects, we suggest measurement of this cytokine in serum of the patients with AR-HIES. On the other hand, in the patients with no mutation in STAT-3 or DOCK-8 genes, investigation of other genes associated with HIES includes SPINK5, PGM-3 and TYK-2 recommended. Also, to ensure the meaningfulness of the results we suggest to include more cases in next studies.

Conclusion

According to the results of the present study, Th17 lymphocytes do not decrease in the patients with AR-HIES. So, the reduction of Th17 lymphocyte population is not the reason of increased susceptibility of these patients to fungal infections.

Conflict of Interest

The authors have declared no conflict of interest.

Acknowledgments

This research was supported by a grant from Pediatric Pathology Research Center, Shahid Beheshti University of Medical Sciences. The authors would like to thank the patients, who participated in this study and Ms. Farah Ghadimi and Ms. Raziyeh Rezaei for their technical laboratory helps.

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