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ORIGINAL ARTICLE

Relation of Serum Interleukin-33 level to Disease Severity in Asthmatic Patients

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ABSTRACT

Background: *Interleukin-33 is a member of IL-1 cytokine family that acts as an important mediator to inflammation in asthma and other allergic diseases.* ***Objective:*** *To study the relation of serum IL-33 level to disease severity in asthmatic patients.* ***Methodology:*** *Serum IL-33 and IgE levels in 40 asthmatic patients and 20 control subjects were measured by ELISA. Patients were classified as having intermittent, mild, moderate or severe asthma. The relation of serum IL-33 to disease severity, serum IgE, presence of atopy and other allergic diseases was evaluated.* ***Results:*** *IL-33 and IgE levels were higher in asthmatic patients compared to controls. These levels showed significant difference in different degrees of disease severity and significant increase in atopic asthmatics compared to non-atopic patients. No difference was found between patients with asthma only and asthmatics with other allergic diseases.* ***Conclusion****: Serum IL-33 is in direct relation to disease severity in asthmatic patients. It is higher in atopic asthmatics than in non-atopic patients.*

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by reversible airway obstruction and bronchial hyperresponsiveness. Recently discovered cytokines as interleukin-33 (IL-33) had been proved to play an important role in the pathogenesis of different allergic conditions. After exposure to allergens, IL-33 producing cells become activated and initiate allergic immune responses in susceptible patients[1]. IL-33 is expressed not only by immune cells, such as dendritic cells, macrophages, and mast cells, but also by non-immune cells, such as epithelial cells, fibroblasts and smooth muscle cells [2].

Interleukin-33 is a cytokine belonging to IL-1 family that stimulates production of Th2 associated cytokines[3]. It is encoded by the IL-33 gene which is located on chromosome 9p24.1[4]. IL-33 interacts with a cell surface heterodimer consisting of an IL-1 receptor-related protein ST2 (IL-1RL1) and IL-1 receptor accessory protein (IL-1RAcP) leading to activation of many immune cells including mast cells, basophils, and Th2 cells, and production of a variety of Th2-like cytokines that mediate allergic-type immune responses[5]. IL-33-induced production of pro-inflammatory cytokines is a critical event that exacerbates atopic diseases such as asthma, atopic dermatitis, and allergic rhinitis [6,7].

In bronchial asthma, IL-33 can contribute to airway remodeling by acting on human lung fibroblasts 8. Its expression increases in the serum, bronchial epithelial cells and bronchoalveolar lavage fluid of bronchial asthma patients 9. The present study was conducted to study the relation of serum interleukin-33 level to disease severity in asthmatic patients.

METHODOLOGY

Study population and design

The study included 40 patients presented to the allergy and immunology clinic of Suez Canal University Hospital (SCUH) with a diagnosis of bronchial asthma. Patients were in the age group of 18 – 60 years. Twenty matching apparently healthy subjects were also included in the study as a control group. Informed consent was taken from each participant in the study.

Detailed medical history was taken from all patients followed by clinical examination and skin prick test. Serum levels of IL-33 and total IgE were measured for each patient and control subject in the study. Based on disease severity, patients were classified into intermittent, mild, moderate and severe asthma according to the National Heart, Lung, and Blood Institute, and National Asthma Education and Prevention Program[10]. They were also classified as atopic and non-atopic according to the results of skin test and total IgE serum levels. Atopy was defined in patients with positive skin test to at least one of the common allergens, elevated serum levels of total IgE and/or association with other atopic conditions as allergic rhinitis and atopic dermatitis. Smokers and patients with chronic diseases or respiratory infections were excluded from the study. The ethics committee of

faculty of medicine, Suez Canal University had reviewed and approved the study.

Measurement of serum IL-33 and total IgE levels

Serum levels of IL-33 and total IgE were measured using commercial ELISA kits (Invitrogen, Thermo Fisher Scientific, USA). The protocol of ELISA was followed according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed using statistical package for social sciences (SPSS) program (Version 17.0). Data were expressed as mean ± standard deviation (SD). The t-test was used to compare the change of parameters. All tests were two tailed, and the level of significance was set at 0.05. Pearson coefficient was used to analyze the correlation between IL-33 and IgE serum levels in asthmatic patients.

RESULTS

The study included 40 asthmatic patients and 20 controls. The age of the patients ranged from 19 to 57 years. Most of them were atopic (80%). Fifty five percent of the patients had asthma only while 45% of them had associated allergic diseases as allergic rhinitis or atopic dermatitis. The demographic data of the studied population are shown in table (1).

Table 1: Demographic data of the studied population

Data	Patients (n=40)	Controls (n=20)	P value
Age in years	38±17.3	37±19.6	NS*
Sex (Male/Female)	17 / 23	8 / 12	NS*
Disease severity			
Intermittent	15 (37.5%)		
Mild	12 (30%)		
Moderate	9 (22.5%)		
Severe	4 (10%)		
Atopy			
Atopic	32 (80%)		
Non-atopic	8 (20%)		
Associated allergic diseases			
Allergic rhinitis	13 (32.5%)		
Atopic dermatitis	5 (12.5%)		
Asthma only	22 (55%)		

*Non-significant

Serum IL-33 level was significantly higher in asthmatic patients compared with controls ($P < 0.001$). Asthmatic patients had also significant higher level of total IgE than controls ($P < 0.05$). Table (2) shows the serum levels of IL-33 and IgE in asthmatic patients and controls. IL-33 and total IgE levels showed significant difference in different degrees of disease severity (Table 3). The correlation between IL-33 and IgE levels showed a significant direct association between them ($P = 0.002$, pearson correlation coefficient (r) = 0.36).

Table 2: Serum IL-33 and total IgE in asthmatic patients and controls

Parameter	Patients (n=40)	Controls (n=20)	P value
Serum IL-33 (pg/ml)	339.2±49.3	135.8 ± 72.3	P<0.001*
Serum total IgE (IU/ml)	181.3±109.4	110.5±121.6	P<0.05*

*Significant

Table 3: Serum IL-33 and total IgE in asthmatic patients with different degrees of disease severity

Disease severity	Serum IL-33 (pg/ml)	Serum total IgE (IU/ml)
Controls	135.8 ± 72.3	110.5 ± 121.6
Intermittent	246.9 ± 61.4	163.5 ± 97.6
Mild	217.4 ± 85.3	153.2 ± 75.7
Moderate	392.5 ± 44.7	185.4 ± 88.9
Severe	518.7 ± 63.2	224.8 ± 51.4
P value	P < 0.001*	P < 0.05*

*Significant

Significant difference was found in the serum level of IL-33 between atopic and non-atopic patients (Table 4). However, there was no significant difference in the serum level of IL-33 between patients with asthma only and asthmatic patients with other allergic diseases as allergic rhinitis or atopic dermatitis (Table 5).

Table 4: Serum IL-33 in atopic and non-atopic patients

Atopic condition	Serum IL-33 (pg/ml)	P value
Atopic	452.3 ± 62.7	P < 0.05*
Non-atopic	377.6 ± 29.5	

*Significant

Table 5: Serum IL-33 in asthmatic patients with/without other allergic conditions

Allergic condition	Serum IL-33 (pg/ml)	P value
Asthma alone	347.4 ± 83.5	
Asthma with allergic rhinitis	396.2 ± 66.4	NS*
Asthma with atopic dermatitis	407.3 ± 28.4	NS*

*Non-Significant

DISCUSSION

Interleukin-33 was identified as a trigger of Th2 cell differentiation, which by interacting with both the acquired and the innate immune responses, can mediate allergy and asthma pathogenesis[11]. This work was conducted to study the relation of serum interleukin-33 level to disease severity in asthmatic patients. It showed that the serum levels of IL-33 were significantly higher in asthmatic patients compared to controls. Similar results were reported by Raeiszadeh et al.[12] who found elevated level of serum IL-33 in asthmatics than in controls 12. Also, the study of Azazi et al[13] showed that the serum levels of both IL-33 and its soluble receptor ST2 were markedly elevated in patients with bronchial asthma compared to the control subjects.

Total IgE serum level also showed significant increase in asthmatic patients compared to control subjects in this study. This agreed with Lama *et al.* 2013 who reported that the serum levels of total IgE were significantly higher in asthmatic subjects compared to non-asthmatics[14]. However, Rahman et al.[15] observed a considerable overlap between serum IgE values of control and asthma groups.

A significant positive correlation between IL-33 and total IgE serum levels was found in the current study. This was in agreement with the study of Momen et al.[16] that found a significant direct correlation between IL-33 and total IgE in asthmatic patients. The study of Mato et al.[17] also stated that IL-33 is closely associated with IgE level and the exacerbation of asthma. However, it was not in agreement with the study of Hastie et al.[18] which reported that serum IL-33 levels show no association with serum total IgE.

The present study showed that serum IL-33 levels were significantly correlated to disease severity in asthmatic patients. This was similar to the study of Bahrami et al.[19] which reported that serum levels of IL-33 were positively correlated to asthma severity**.** The study of Guo *et al.*[8] stated that IL-33 is a marker of asthma severity**.** Hamzaoui et al.[20] measured IL-33 levels in the induced sputum of asthmatic children and reported that levels of IL-33 were in positive correlation with disease activity**.** Total IgE serum levels were also correlated with disease severity in asthmatic patients included in the current study. It was in accordance with the study of Kumar *et al.*[21] that reported a significant association between elevated serum IgE and severe persistent asthma**.** However, it was not in accordance with Davila *et al.*[22] who did not find a significant association between serum total IgE levels and asthma severity or airflow limitation**.** Moore *et al.*[23] also showed no correlation between asthma severity and levels of total and antigen-specific IgE**.**

In the present study, serum levels of IL-33 showed significant increase in atopic patients compared to non-atopic patients. This was in accordance with the study of Mato et al.[17] which reported that atopic asthmatic patients had significantly higher serum levels of IL-33 than non-atopic patients**.** However, no significant difference was found in the serum levels of IL-33 between patients with asthma only and asthmatic patients with other allergic diseases as allergic rhinitis or atopic dermatitis. This was in agreement with the study of Momen et al.[16] that found no significant differences in the serum levels of IL-33 in asthmatic patients with or without allergic rhinitis or atopic dermatitis**.** Several studies had proved the role of IL-33 in some allergic diseases such as allergic rhinitis, atopic dermatitis, and allergic conjunctivitis[24-26].

The results of the current study approved that serum IL-33 level is in direct correlation to disease severity and serum total IgE level in asthmatic patients. Serum IL-33 levels show significant increase in atopic asthmatics compared to non-atopic patients. Further studies are required to confirm the role of this cytokine as a therapeutic target in asthma and other allergic diseases.

REFERENCES

1. Gupta RK, Gupta K, Dwivedi PD. Pathophysiology of IL-33 and IL-17 in allergic disorders. Cytokine Growth Factor Rev. 2017 Dec; 38:22-36.
2. Nakae S, Morita H, Ohno T, Arae K, Matsumoto K, Saito H. Role of interleukin-33 in innate-type immune cells in allergy. Allergol Int. 2013; 62:13-20.
3. Yagami A, Orihara K, Morita H, Futamura K, Hashimoto N, Matsumoto K, *et al.* IL-33 mediates inflammatory responses in human lung tissue cells. Journal of immunology. 2010; 185 (10):5743-50.
4. Zlatko Dembic. Cytokines of the Immune System: Interleukins. In: The Cytokines of the Immune System. Academic Press. 2015; Chapter 6, 143-239.
5. Saluja R, Ketelaar ME, Hawro T, Church MK, Maurer M, Nawijn MC2. The role of the IL-

33/IL-1RL1 axis in mast cell and basophil activation in allergic disorders. Mol Immunol. 2015 Jan; 63(1):80-5.
6. Nabe T. Interleukin (IL)-33: new therapeutic target for atopic diseases. J Pharmacol Sci. 2014; 126(2):85-91.
7. Du Y, Luo Y, Yang C, Liu J, Wan J, Wang K. Discussion IL-33 and its receptor ST2 associated with the pathogenesis of allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2015 May; 29(9):811-4.
8. Guo Z, Wu J, Zhao J, Liu F, Chen Y, Bi L, *et al.* IL-33 promotes airway remodeling and is a marker of asthma disease severity. J Asthma. 2014 Oct; 51(8):863-9.
9. Préfontaine D, Nadigel J, Chouiali F, Audusseau S, Semlali A, Chakir J, *et al.* Increased IL-33 expression by epithelial cells in bronchial asthma. J Allergy Clin Immunol. 2010 Mar; 125(3):752-4.
10. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Bethesda: National Heart, Lung, and Blood Institute; 2007. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Available at: .www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf
11. Makrinioti H, Toussaint M, Jackson DJ, Walton RP, Johnston SL. Role of interleukin 33 in respiratory allergy and asthma. Lancet Respir Med. 2014 Mar; 2(3):226-37.
12. Raeiszadeh JS, Mahesh PA, Jayaraj BS, Madhunapantula SR, Holla AD, Vishweswaraiah S, Ramachandra NB. Serum levels of IL-10, IL-17F and IL-33 in patients with asthma: a case-control study. J Asthma. 2014 Dec; 51(10):1004-13.
13. Azazi EA, Elshora AE, Tantawy EA, Elsayd MA. Serum levels of interleukin-33 and its soluble receptor ST2 in asthmatic patients. Egypt J Chest Dis. 2014; 63:279–84.
14. Lama M, Chatterjee M, Chaudhuri TK. Total Serum Immunoglobulin E in Children with AsthmaIndian J Clin Biochem. 2013; 28(2): 197–200.
15. Rahman MA, Ahmed S, Islam MT, Rahaman MF. Total Serum IgE Level Estimation in Asthma Patient and Healthy Volunteers in a Tertiary Care Hospital, Bangladesh. Mymensingh Med J. 2016 Jan; 25(1):126-31.
16. Momen T, Ahanchian H, Reisi M, Shamsdin SA, Shahsanai A, Keivanfar M. Comparison of Interleukin-33 Serum Levels in Asthmatic Patients with a Control Group and Relation with the Severity of the Disease. Int J Prev Med. 2017; 8: 65.
17. Mato N, Bando M, Yamasawa H, Hosono T, Mizushina Y, Sata M, *et al.* Role of IL-33 in bronchial asthma. Nihon Kokyuki Gakkai Zasshi. 2010 Jun; 48(6):419-25.
18. Hastie AT, Rector B, Moore WC, Li H, Peters SP, Meyers DA, Bleecker ER. Serum and Sputum Interleukin-33 (IL-33) Levels Show No Association With Serum Total IgE, Positive Skin Test Number, Exhaled Nitric Oxide, or Increasing Severity of Atopic Asthma. American Journal of Respiratory and Critical Care Medicine 2013; 187:A1008
19. Bahrami MS, Movahedi M, Aryan Z, Bahar MA, Rezaei A, Sadr M, Rezaei N; Universal Scientific Education and Research Network (USERN). Serum IL-33 Is Elevated in Children with Asthma and Is Associated with Disease Severity. Int Arch Allergy Immunol. 2015; 168(3):193-6.
20. Hamzaoui A, Berraies A, Kaabachi W, Haifa M, Ammar J, Kamel H. Induced sputum levels of IL-33 and soluble ST2 in young asthmatic children. J Asthma. 2013; 50:803–9
21. Kumar RM, Pajanivel R, Koteeswaran G, Menon SK, Charles PM. Correlation of total serum immunoglobulin E level, sputum, and peripheral eosinophil count in assessing the clinical severity in bronchial asthma. Lung India. 2017 May-Jun; 34(3):256-261.
22. Davila I, Valero A, Entrenas LM, Valveny N, Herráez L; SIGE Study Group. Relationship between serum total IgE and disease severity in patients with allergic asthma in Spain. J Investig Allergol Clin Immunol. 2015; 25(2):120-7.
23. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, *et al.* Characterization of the severe asthma phenotype by the national heart, lung, and blood institute's severe asthma research program. J Allergy Clin Immunol. 2007; 119:405–413.
24. Wang Y, Li C, Luo X, Xu D, Xu Y, Li G, *et al.* Interleukin-33 promotes helper T cell type-2/17 inflammation in children with allergic rhinitis. Eur Arch Otorhinolaryngol. 2017 Nov 17. Epub ahead of print
25. Matsuda A, Okayama Y, Terai N, Yokoi N, Ebihara N, Tanioka H, *et al.* The role of interleukin-33 in chronic allergic conjunctivitis. Invest Ophthalmol Vis Sci. 2009; 50:4646–52.
26. Savinko T, Matikainen S, Saarialho-Kere U, Lehto M, Wang G, Lehtimäki S, *et al.* IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. J Invest Dermatol. 2012; 132(5):1392-400.