ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALERJİ İMMÜNOLOJİ

doi: 10.21911/aai.296
Asthma Allergy Immunol 2023;21:207-214

RESEARCH ARTICLE

Received: 15.05.2023 • Accepted: 07.11.2023
Online Published: 04.12.2023

Differential Diagnosis of Patients with Total Serum Immunoglobulin E Above 2000 IU/L

Azize Pinar METBULUT[1], Harun SIVLIM[2], Ilknur KULHAS CELIK[1], Ayse METIN[1], Emine DIBEK MISIRLIOGLU[1], Muge TOYRAN[1], Ersoy CIVELEK[1]

[1] Division of Pediatric Allergy and Immunology, Health Sciences University, Ankara City Hospital, Ankara, Turkey
[2] Department of Pediatrics, Bayburt State Hospital, Bayburt, Turkey

Corresponding Author: Azize Pınar Metbulut ✉ pinar298@yahoo.com

ABSTRACT

Objective: Allergic diseases, infections, parasitic infections, hematologic malignancies, chronic lung diseases, inflammatory diseases, cystic fibrosis, nephrotic syndrome and primary immunodeficiencies (PIDs) are the main disorders in the differential diagnosis of elevated serum IgE levels.

The aim of this study was to evaluate the differential clinical diagnosis of patients whose serum IgE levels were found to be above 2000 IU/ml when measured at the pediatric allergy and immunology outpatient clinics of our hospital.

Materials and Methods: This was a retrospective study of children aged between 2 months to 18 years referred to the Pediatric Allergy and Immunology clinics and evaluated at our hospital between October 2010 and March 2021.

Results: In the 480 patients with serum total IgE levels exceeding 2000 IU/ml in this study, allergic diseases were observed in 313 (65.2%) patients, primary immunodeficiencies in 28 (5.8%), infectious diseases in 12 (2.4%), hematological diseases in 14 (2.8%), rheumatologic diseases in 5 (1%), and other diseases in 2 (0.4%), while 113 (23.5%) patients were undefined.

Conclusion: This study revealed that allergic diseases were the most common cause of extremely elevated serum IgE levels, while 5.8% of the patients were diagnosed with primary immunodeficiencies. Our study indicates that primary immunodeficiencies, although rare, should be kept in mind in patients with a serum total IgE above 2000 IU/ml.

Keywords: Total IgE, child, differential diagnosis

INTRODUCTION

Immunoglobulin E (IgE) elevation is a common laboratory result in pediatric outpatient clinics, and it can sometimes concern families and doctors. In daily practice, some of the patients evaluated in allergy and immunology outpatient clinics consists of patients with an elevated serum total IgE level. Although serum total IgE elevation may suggest the presence of an allergic disease at first glance, it may actually be elevated due to many different clinical conditions (1). Allergic diseases, infections, especially parasitic infections, hematologic malignancies, chronic lung diseases, inflammatory diseases, cystic fibrosis, nephrotic syndrome, and primary immunodeficiencies (PIDs) are considered in the differential diagnosis of elevated IgE levels (1-3).

Variations in the upper limit of normal serum total IgE have been reported to range from 150 to 1,000 UI/ml; but the commonly accepted upper limit is between 150 and 300 UI/ml (4). Since serum total IgE concentrations vary significantly with age, age-specific reference ranges have been established for both children and adults (5).

IgE elevation may be an important laboratory finding of the primary immunodeficiencies, and IgE may be elevated especially in five groups of PIDs: Hyper-IgE syndrome

ORCID Azize Pinar Metbulut / 0000-0001-8823-5960, Harun Sivlim / 0000-0003-3184-5519, Ilknur Kulhas Celik / 0000-0003-3812-9654, Ayse Metin / 0000-0003-2261-4364, Emine Dibek Misirlioglu / 0000-0002-3241-2005, Müge Toyran / 0000-0002-2490-0551, Ersoy Civelek / 0000-0002-1780-4801

(HIES), Wiskott-Aldrich syndrome; immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX); Omenn syndrome; and atypical complete DiGeorge syndrome (6). In the literature, the frequency of primary immunodeficiency in patients with a serum IgE level of 2000 IU/ml and above has been investigated in very few studies, and these studies evaluated small patient groups.

Allergic patients have elevated antigen-specific and total serum IgE levels (1,000- 10,000 IU/mL) (7). Markedly elevated serum total IgE levels have been rarely observed in allergic rhinitis, asthma, and atopic dermatitis (8). The serum IgE level has been found to correlate with the severity of the underlying allergic disease, especially in allergic rhinitis and asthma (9,10).

The aim of this study was to evaluate the differential clinical diagnosis of patients whose serum IgE levels were measured in the pediatric allergy and immunology outpatient clinics of our hospital and found to be above 2000 IU/ml.

MATERIALS and METHODS

This was a retrospective study of children aged 2 months to 18 years who were referred to the Pediatric Allergy and Immunology Clinics and evaluated in our hospital between October 2010 and March 2021. Patients who had a serum IgE level measured above 2000 IU/ml at least once were involved in this study. The study protocol was approved by the Institutional Ethics Committee (E2-21-690).

Patients with symptoms of allergic diseases, parasitic infections (such as abdominal pain, diarrhea, nausea, vomiting), rheumatologic diseases (arthralgia, fever, weight loss, fatigue, tenderness and stiffness of the joints), malignancies (such as weight loss, fever) and immunodeficiencies were evaluated with the serum total IgE level. IgE measurements were performed with an IMMAGE 800 Immunochemistry System using the nephelometric method, and values were expressed as IU/ml. The method was consistently used in the past ten years.

Medical history and demographic information such as the age, gender, patient history and family history of chronic and allergic diseases, symptoms, and physical examination findings were acquired from the hospital records. Laboratory tests were performed at the point of clinical diagnosis and when necessary. Laboratory data was also recorded, when available.

Parameters included in the initial diagnostic workup for hyperimmunoglobulin E were recorded, when available, such as liver and kidney function tests, allergy test results such as the skin prick test and serum-specific IgE level, and stool/serology for parasites. For skin prick tests, the food and/or inhaler allergens recommended in the European Academy of Allergy and Clinical Immunology according to the history were used in the test panel (11). Tests for evaluating the immunodeficiencies (such as serum immunoglobulin levels and peripheral blood lymphocyte subset analysis) were recorded, when available. Imaging tests (such as computed tomography of the chest, abdomen, and pelvis; electrocardiogram, echocardiogram, ultrasonography) were performed if needed.

The reason for using a serum IgE level of >2000 IU/ml was that one of the items in the HIES score is an elevated serum IgE level >2000 IU/ml (12).

Statistical Analysis

The results were expressed as percentile (absolute numbers), as mean and standard deviation, or as median and interquartile range (IQR), as required. Statistical Product and Service Solutions 22 (SPSS) (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS

A total of 480 patients including 135 (28.1%) males were evaluated. The median age of the children for which serum IgE analysis was performed was 91 months (IQR: 47.2-143 months). The clinical diagnoses of the patients with elevated serum IgE is shown in Figure 1. Among the

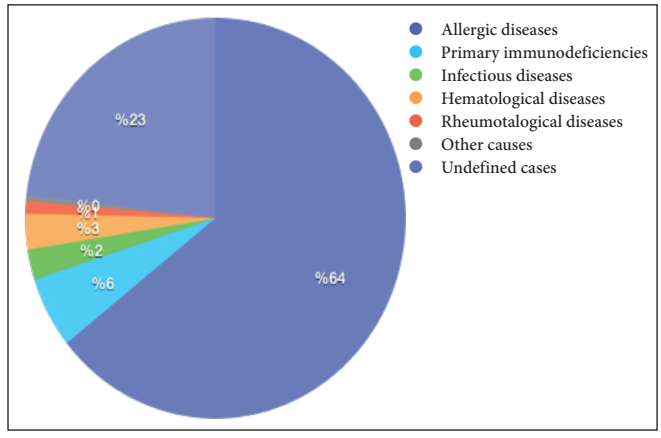

Figure 1. Clinical diagnosis of patients with elevated serum total IgE.

480 patients, the most common chronic disease was asthma (152 [31.7%]). The family of 57 (11.9%) of the patients had a history of allergic disease, and none of the patients had an immunodeficiency disease. At the first presentation, 135 (28.1%) had pathological findings on physical examination (Table I).

Allergic Diseases

An allergic disease was diagnosed in 313 of the 480 patients (65.2%). The most common allergic disease was asthma. The second and third most common allergic diseases were allergic rhinitis and food allergy (Table II). Skin prick tests were performed in 243 (50.6%) patients. Atopy was detected in 174 (71.6%) patients. Pollen was the most common aeroallergen observed at a rate of 43.6% (n:106). In 87 (18.1%) patients, specific IgE titers were measured, and inhaled allergen positivity was the most common detected condition.

Immunologic Diseases

Immunodeficiency was diagnosed in 28 (5.8%) patients. Hyper-IgE sydrome (HIES) was diagnosed in 9 (1.9%) patients. Among these patients, DOCK8 (Dedicator of and Cytokinesis 8) and STAT3 (Signal transducer and activator of transcription 3) mutations were detected in 5 (1%) and 2 (0.4%) patients, respectively. Mutation analyses are still pending in another two patients with possible HIES according to the NIH-HIES score. Other immunodeficiencies diagnosed with IgE elevation were chronic granulomatous disease (CGD) (2 [0.4%]), severe combined immunodeficiency (SCID) with the Omenn phenotype (2 [0.4%]), immune dysregulation polyendocrinopathy, enteropathy X-linked syndrome (IPEX) (2 [0.4%]), autoimmune lymphoproliferative syndrome (ALPS) (1 [0.2%]), common variable immune deficiency /CVID) (1 [0.2%]), Griscelli syndrome (1 [0.2%]), Kostmann syndrome (1 [0.2%]), IL-21 receptor deficiency (1 [0.2%]), IL-17F mutation (1 [0.2%]), selective IgA defi-

Table I: Demographic and clinical characteristics of patients with elevated serum total IgE.

	Patients with elevated serum total IgE (>2000 IU/ml))
Age (months), median (IQR)	91 (47.2-143)
Gender (female/male)	2/5
Male, n (%)	135 (28.1)
Consanguinity, n (%)	35 (7.3)
Preterm, n (%)	9 (1.9)
Cesarean section, n (%)	39 (8.1)
Having concomitant chronic disease at presentation, n (%)	93 (19.4)
Using medication at presentation, n (%)	113 (23.5)
Having a pathology on physical examination at presentation, n (%)	135 (28.1)
Atopy status	
Skin prick test performed, n (%)	243 (50.6)
Having aeroallergen sensitization, n (%)	174 (71.6)

Table II: Clinical diagnosis of patients with elevated serum total IgE.

The primary clinical diagnosis	
Allergic diseases, n (%)	313 (65.2)
Asthma	152 (31.7)
Allergic Rhinitis	88 (18.3)
Atopic Dermatitis	62 (12.9)
Food Allergy	66 (13.8)
Single food trigger	35 (7.3)
Multiple food triggers	31 (6.5)
Chronic urticaria	17 (3.5)
Anaphylaxis	10 (2.1)
Food-related anaphylaxis	7 (1.5)
Drug-related anaphylaxis	2 (0.4)
Vaccine-related anaphylaxis	1 (0.2)
Drug Allergy	7 (1.5)
Venom Allergy	3 (0.6)
Allergic Contact Dermatitis	1 (0.2)
Primary immunodeficiencies, n (%)	28 (5.8)
Infectious diseases, n (%)	12 (2.4)
Parasitic infections	6 (1.2)
Hydatid cyst	3 (0.6)
Fasciola hepatica	2 (0.4)
Blastocystis hominis	1 (0.2)
Other enfestations	10 (2.1)
Hematological diseases, n (%)	14 (2.8)
Malignancies, n (%)	10 (2)
Leukemia	5 (1)
Lymphoma	3 (0.6)
Hodgkin lymphoma	2 (0.4)
Large cell anaplastic lymphoma	1 (0.2)

ciency (4 [0.8%]), and selective IgM deficiency (4 [0.8%]). The primary clinical diagnoses are presented in Table III.

Infectious Diseases

Infectious diseases were observed in 12 (2.4%) patients. The most common was parasitic infestation at a rate of 1.2% (n:6). Hydatid cyst was observed in 3 (0.6%) patients with 2 of them detected in the lung and 1 of them in the brain. Blastocystis hominis and fasciola hepatica were detected in 2 (0.4%) patients and 1 (0.2%) patient, respectively. Eosinophilic folliculitis, Herpes simplex encephalitis, impetigo, scabies, varicella, sinusitis, cystic fibrosis activation and, HPV-induced epidermodysplasia verruciformis were observed in one patient each (0.2% each) (Table II). Stool tests were performed due to the suspicion of parasites in 92 (19.2%) patients, and a positive test result was found only in 7 (1.5%). A total of 25 (5.2%) patients were treated with antiparasitic drugs that were given empirically. None of the serologic tests for parasites gave a positive result.

Other Diseases

Hematologic diseases were observed in 14 (2.8%) patients. Malignancies were detected in 10 (2%), patients. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) were detected in 4 (0.8%) patients and 1 (0.2%) patient respectively. Hodgkin lymphoma, Langerhans cell histiocytosis, and large cell anaplastic lymphoma were detected in 2 (0.4%), 2 (0.4%) and 2 (0.2%) patients, respectively. Immune thrombocytopenic purpura (ITP), B12 deficiency, thalassemia major, and cyclic neutropenia were detected in 1 (0.2%) patient each. Rheumatologic diseases were observed in 5 (1%) patients. Systemic lupus erythematosus (SLE), Crohn disease, Juvenile idiopathic arthritis (JIA), and autoimmune hepatitis were detected in 2 (0.4%), 1 (0.2%), 1 (0.2%) and 1 (0.2%) patients, respectively (Table II). Laboratory findings of the patients are shown in Table IV.

Invasive diagnostic tests were also performed as needed. Pathological findings were detected in bronchoscopy in one (0.2%) patient and defined as narrowness at the lingula. Bone marrow aspiration was performed in 3 (0.6%) patients and only 1 of them revealed hypereosinophilia in the bone marrow. Skin biopsy was performed in 2 (0.4%) patients and one of them reported a pathological result defined as eosinophilic folliculitis. Despite all the diagnostic tests were performed, no diagnosis could be made in 113 (23.5%) patients.

Table III: Clinical diagnosis of patients with a diagnosis of immunodeficiency with a serum IgE level above 2000 IU/ml.

Immunodeficiencies, n (%)	28 (5.8)
Hyper IgE syndrome	9 (1.9)
DOCK8 deficiency	5 (1)
STAT3 deficiency	2 (0.4)
Undefined (mutation unknown) HIES	2 (0.4)
Chronic granulomatous disease	2 (0.6)
Selective IgA deficiency	4 (0.8)
Selective IgM deficiency	2 (0.4)
Hyper IgM syndrome	1 (0.2)
Severe combined immunodeficiency	2 (0.4)
JAK3 mutation - Omenn syndrome	1 (0.2)
RAG2 mutation - Omenn syndrome	1 (0.2)
Common variable immunodeficiency	1 (0.2)
Autoimmune lymphoproliferative syndrome	1 (0.2)
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome	2 (0.4)
Griscelli syndrome	1 (0.2)
Kostmann syndrome	1 (0.2)
IL-21 deficiency	1 (0.2)
IL-17-mutation	1 (0.2)

Table IV: Laboratory Findings of the patients.

Laboratory finding, mean	
Total white blood cell count	8608
Serum hemoglobin level	12.7
Serum neutrophil level (absolute number)	4097
Serum lymphocyte level (absolute number)	3155
Serum eosinophil level (absolute number)	628
Serum eosinophil level (percent)	6.5
Serum platelet level	330.000
AST level	33.5
ALT level	23
Serum urine level	25.6
Serum creatinine level	0.52
Serum IgG level	1192
Serum IgM level	113
Serum IgA level	142.6
Total IgE level, median, IQR	2792, 2240-4196

DISCUSSION

Among the 480 patients with serum IgE levels exceeding 2000 IU/ml in our study, allergic diseases were observed in 313 (65.2%) patients, primary immunodeficiencies in 28 (5.8%), infectious diseases in 12 (2.4%), hematological diseases in 14 (2.8%), rheumatologic diseases in 5 (1%), and other diseases in 2 (0.4%) patients while 113 (23.5%) patients were undefined (Table II).

The most common clinical diagnosis was allergic disease, with a rate of 65.2% (n:313), and most commonly asthma (152 [31.7%]) in our patients. The second and third most commonly diagnosed allergic diseases were allergic rhinitis (18.3%) and atopic dermatitis (12.9%).

High IgE is a indicator of atopy (1). Atopy is the genetic predilection to produce specific IgE following exposure to allergens. At the cellular level, atopy appears to result, in part, from a predisposition toward a certain response on the part of CD4+ T helper cells called the T helper type 2 (Th2) response (13). Th2 cells secrete large quantities of interleukin-4 (IL-4) and interleukin-13 (IL-13), which promote the production of allergen-specific IgE by plasma cells (14).

According to Joshi et al., the most commonly diagnosed diseases were allergic diseases with a rate of 77% (n=54) among the 70 patients with serum IgE levels above 2000 IU/ml followed between 1997 and 2006, and asthma was the most common one in pediatric patients (15). Serum IgE can be even higher than 2000 IU/ml in allergic diseases. According to Kıykım et al, the serum IgE level was between 27 and 7122 IU/ml in atopic dermatitis, between 4-3000 IU/ml in allergic asthma, and between 71-1969 IU/ml in allergic rhinitis in their study group. It was observed that the cut-off values for discriminating atopic diseases from HIES were 2500 IU/l for IgE and 1500/mm^3 for eosinophils with ROC curve analysis (16). Extreme serum IgE levels were detected in allergic rhinitis by Hyun et al. and Lin et al. (17,18). According to Ng et al., 133 patients had a serum total IgE level higher than 2000 IU/ml among 330 pediatric atopic dermatitis patients. In these patients, hyper-IgE levels were observed to be associated with asthma, severe eczema, and dust mite atopy (19). In another study, it was observed that the serum IgE level in atopic dermatitis patients was between 1011 and 3015 IU/ml (20). According to Tanaka et al., the serum IgE level in patients with asthma was observed to be maximum of 2891 IU/ml (10). Louis et al. reported a serum total IgE level of 17-7620 IU/ml among 41 adult asthma patients (21).

Some patients with allergic diseases have non-elevated serum total IgE levels (22-27). However, most of the IgE levels higher than 2000 IU/ml in our study were observed to be related with allergic diseases.

Among 480 patients whose serum IgE levels were above 2000 IU/ml, 28 (5.8%) patients were diagnosed as primary immunodeficiency disease. According to Ponsford et al., the prevalence of immunodeficiencies was observed to be below 1% in patients with a serum IgE level above 1000 IU/ml in a tertiary care center (2). According to Joshi et al., HIES was diagnosed in 9% (n=6) of the 70 pediatric patients whose serum IgE levels were observed to be above the 2000 IU/ml in a 10-year period (15). The number of patients diagnosed as PID with extremely high IgE levels was 9 (1.9%) in our study.

Mechanisms of IgE elevation were explained with defective IFN-gamma and IL-10 production in PIDs, and reduced Treg cells, T cell oligoclonality, and increased IL-4 production in Treg cell deficiencies. A defective Treg cell number or function results in autoimmunity and a TH2 phenotype with increased IgE levels (6). Extreme elevation of IgE has relevance to primary immunodeficiencies (PID) such as SCID with Omenn phenotype and other defects in T-cell development. PID diseases associated with IgE >1000 IU/ml have been reported as follows in the literature: impaired TCR signalling and cytoskeletal remodelling (WAS, DOCK8 deficiency, CARD11), cytokine signalling defects (STAT3, Loey-Dietz syndrome, STAT5b, IRAK4, Myd88 deficiencies), immune dysregulation diseases (IPEX, FAS-FASL, caspase 8-10 defects, ALPS), congenital defects of phagocyte function (chronic granulomatous disease), polygenic disorders (selective IgA deficiency), barrier defect (such as the Comel-Netherthon syndrome, loss of filaggrin, severe skin dermatitis, multiple allergies and metabolic wasting [SAM syndrome]) (2,6).

In our study, there were eight patients diagnosed with immunodeficiencies, with serum IgE elevation above 2000 IU/ml that was detected by chance or as an important component of the disease. These diseases are autoimmune lymphoproliferative syndrome (ALPS), common variable immune deficiency /CVID), Griselli syndrome, Kostmann syndrome, IL-21 receptor deficiency, and IL-17F mutation, each detected in 1 (0.2%) patient. Selective

IgA deficiency and selective IgM deficiency were observed in 4 (0.8%) and 2 (0.4%) patients, respectively (Table II). In several case studies, the maximum serum IgE levels observed in were as high as 100.000 IU/ml in HIES, 3698 IU/ml in IPEX patients (28), 5030 IU/ml in WAS patients [30], 2600 -6330 IU/ml in ALPS patients (29, 30), 5030 IU/ml in chronic granulomatous disease (31), 35.000 IU/ml in Comel- Netherthon syndrome patients (32), 1040 IU/ml in Griselli syndrome patients (33) and 2110 IU/ml in selective IgM deficiency patients were detected in the literature (34).

Even if immunodeficiency associated with IgE elevation is not suspected, the evaluation of unexplained IgE elevations by an experienced clinical immunologist may be important to complete the diagnostic approach. Therefore, this group of patients should be referred to immunology departments.

According to Lawrence, elevations in serum IgE were seen in both polygenic allergic diseases such as atopic dermatitis and food allergy, and in a growing list of monogenic primary immunodeficiencies (35). Among the patients with immunodeficiencies in our study, 8 (28.5%) patients had additional allergic diseases. and 5 (55.6%) diagnosed with OR-HIES (Dock8 deficiency) were observed to have concomitant food allergies. Asthma, atopic dermatitis, food allergy with multiple-triggering, anaphylaxis, and drug allergy were detected in 2 (22.2%), 2 (22.2%), 3 (33.3%), 2 (22.2%), and 1 (11.1%) patients diagnosed with HIES, respectively.

The necessity to investigate infectious diseases, rheumatological diseases, and malignancy should always be remembered when unexplained IgE elevation is present (1). Helminth allergens are potent stimulators of the IgE-mediated immune response. High IgE response to tissue-invading parasitic infections is accompanied by high IL-4, IL-5, and IL-13 levels, high peripheral blood and tissue eosinophil counts, as well as high mast cell counts (1). A study has reported that total IgE elevation was seen in 50% of these patients (36). In our study, 10 (2%) patients were diagnosed with parasitic infestations, all with hydatid cyst disease.

There is a group of patients where the cause of high IgE levels cannot be determined despite detailed investigations. It is still unknown why the serum total IgE level was elevated in these patients during follow-up. In a healthy population lacking a personal or family history of allergy, the influence of genetic factors (family history of allergy), environmental factors (degree of air pollution), age, and sex have been observed to influence the serum total IgE levels (37). Serum total IgE levels were rarely observed to be high in healthy children and adults (38). Further studies are needed.

According to Joshi et al., there were patients with no correlation between the serum IgE level and diagnosis of allergic diseases, Hyper-IgE syndromes, malignancy, and parasitic diseases. In 70 patients with a serum IgE level above 2000 IU/ml, 7 remained undiagnosed (15).

The limitation of this study was that it was retrospective; however, the strength was having the highest number of patients with an IgE level above 2000 IU/ml in the literature.

In conclusion, allergic diseases were found to be the most common cause of extremely elevated serum IgE levels in this study. While 5.8% of the patients were diagnosed with primary immunodeficiencies, our study indicates that primary immunodeficiencies, although rare, should be considered in patients with a serum IgE above 2000 IU/ml.

Conflict of Interest

The authors report no conflicts of interest.

Authorship Contributions

Concept: **Ersoy Civelek,** Design: **Ersoy Civelek, Ilknur Kulhas Celik,** Data collection or processing: **Azize Pinar Metbulut, Harun Sivlim, İlknur Külhaş Çelik,** Analysis or Interpretation: **Ayşe Metin Müge Toyran, Emine Dibek Misirlioglu,** Literature search: **Azize Pinar Metbulut, Ersoy Civelek,** Writing: **Azize Pinar Metbulut,** Approval **Ersoy Civelek, Muge Toyran, Ayse Metin, Emine Dibek Misirlioglu.**

REFERENCES

1. Salo PM, Calatroni A, Gergen PJ, Hoppin JA, Sever ML, Jaramillo R, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2011;127(5):1226-35.
2. Ponsford MJ, Klocperk A, Pulvirenti F, Dalm VASH, Milota T, Cinetto F, et al. Hyper-IgE in the allergy clinic—when is it primary immunodeficiency? Allergy 2018;73(11):2122-36.
3. Stone KD, Prussin C, Metcalfe DD. IgE, Mast cells, Basophils, and Eosinophils. J Allergy Clin Immunol 2010;125(2 Suppl 2):S73–S80.

4. Laurent J, Noirot C, Ansquer JC, Laurent G, Kestenbaum S, Lagrue G. How to define the normal level of serum IgE in adults?. Ann Med Interne 1985;136(5):419-22.
5. Martins TB, Bandhauer ME, Bunker AM, Roberts WL, Hill HR. New childhood and adult reference intervals for total IgE. J Allergy Clin Immunol 2014;133(2):589-91.
6. Ozcan E, Notarangelo LD, Geha RS. Primary immunodeficiencies with aberrant IgE production. J Allergy Clin Immunol 2008;122(6):1054-62.
7. Grimbacher B, Belohradsky BH, Holland SM. Immunoglobulin E in primary immunodeficiency diseases. Allergy 2002;57:995-1007.
8. Altaii HA, Al-Tae FMD. Investigation of Serum Total IgE and Eosinophil Levels in Different Allergic Diseases Together with the Study of Their Correlations with Various Possible Allergens in Mosul City. Immunol Invest 2022;51(3):567-87.
9. Ciprandi G, Comite P, Ferrero F, Fontana V, Bruzzone M, Mussap M. Serum allergen-specific IgE, allergic rhinitis severity, and age. Rhinology 2016;54(3):231-8.
10. Tanaka A, Jinno M, Hirai K, Miyata Y, Mizuma H, Yamaguchi M, et al. Longitudinal increase in total IgE levels in patients with adult asthma: an association with poor asthma control. Respir Res 2014;20;15(1):144-52.
11. Klimek L, Hoffmann HJ, Kalpaklioglu AF, Demoly P, Agache I, Popov TA, et al. In-vivo diagnostic test allergens in Europe: A call to action and proposal for recovery plan-An EAACI position paper. Allergy 2020;75(9):2161-9.
12. Szczawinska-Poplonyk A, Kycler Z, Pietrucha B, Heropolitanska-Pliszka E, Breborowicz A, Gerreth K. The hyperimmunoglobulin E syndrome - clinical manifestation diversity in primary immune deficiency. Orphanet J Rare Dis 2011;15;6:76-87.
13. Borish L. Allergic rhinitis: systemic inflammation and implications for management. J Allergy Clin Immunol 2003;112:1021-1.
14. Stokes Jeff, Casale TB. The relationship between IgE and allergic disease. UpToDate. Feb 2022.
15. Joshi AY, Iyer VN, Boyce TG, Hagan JB, Park MA, Abraham RS. Elevated serum immunoglobulin E (IgE): When to suspect hyper-IgE syndrome-A 10 year pediatric tertiary care center experience. Allergy Asthma Proc 2009;30:23-27.
16. Kıykım A, Yüce EG, Barış E, Nain E, Keleş S, Aktürk H, et al. Can Atopic Diseases be Differentiated from Hyper IgE Syndrome by Serum IgE and Blood Eosinophil Levels?. Asthma Allergy Immunology 2017;15:73-81.
17. Lin IH, Tsai MC, Chen JP, Fu LS. Allergic children with extremely high total IgE but no allergen identified in the initial screening panel. J Microbiol Immunol Infect 2021;54(3):474-81.
18. Hyun DW, Min HJ, Kim MS, Whon TW, Shin NR, Kim PS, et al. Dysbiosis of Inferior Turbinate Microbiota Is Associated with High Total IgE Levels in Patients with Allergic Rhinitis. Infect Immun 2018;22;86(4):e00934-17.
19. Ng C, Hon KL, Kung JS, Pong NH, Leung TF, Wong CK. Hyper IgE in childhood eczema and risk of asthma in Chinese children. Molecules 2016;10;21(6):753-60.
20. Wakamori T, Katoh N, Hirano S, Kishimoto S, Ozasa K. Atopic dermatitis, dry skin and serum IgE in children in a community in Japan. Int Arch Allergy Immunol 2009;149(2):103-10.
21. Louis R, Pilette C, Michel O, Michils A, Brusselle G, Poskin A, et al. Variability in total serum IgE over 1 year in severe asthmatics. Allergy Asthma Clin Immunol 2019;15:20-9.
22. Karli R, Balbaloglu E, Uzun L, Cinar F, Ugur MB. Correlation of symptoms with total IgE level and specific IgE levels in patients with presenting with allergic rhinitis. Ther Adv Respir Dis 2013;7(2):75-9.
23. Wong CY, Yeh KW, Huang JL, Su KW, Tsai MH, Hua MC, et al. Longitudinal analysis of total serum IgE levels with allergen sensitization and atopic diseases in early childhood. Nature 2020(10):2127-33.
24. Park HJ, Kim EJ, Yoon D, Lee JK, Chang WS, Lim YM, et al. Prevalence of self-reported allergic diseases and IgE levels: A 2010 KNHANES analysis. Allergy Asthma Immunol Res 2017;9(4):329-39.
25. Tu YL, Chang SW, Tsai HJ, Chen LC, Lee WI, Hua MC, et al. Total serum IgE in a population-based study of Asian children in Taiwan: Reference value and significance in the diagnosis of allergy. PLoS One 2013;8(11):e80996.
26. Mediaty A, Neuber K. Total and specific serum IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy but not in patients with atopic dermatitis. Immun Ageing 2005;31;2(1):9-13.
27. Woszczek G, Kowalski ML, Borowiec M. Association of asthma and total IgE levels with human leucocyte antigen-DR in patients with grass allergy. Eur Respir J 2002;20(1):79-85.
28. Jamee M, Zaki-Dizaji M, Lo B, Abolhassani H, Aghamahdi F, Mosavian M, et al. Clinical, Immunological, and Genetic Features in Patients with Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) and IPEX-like Syndrome. J Allergy Clin Immunnol 2020;8(8):2747-2760.e7.
29. Gülle S, Gülen H, Ağın H, et al. A Case of autoimmune lymphoproliferative Syndrome with Kimura's Disease Like Histopathology. Turkiye Klinikleri J Pediatr 2009;18(4):345-8.
30. Kim YJ, Dale JK, Noel P, Brown MR, Nutman TB, Straus SE, et al. Eosinophilia is Associated with a Higher MortalityRate Among Patients With Autoimmune Lymphoproliferative Syndrome. Am J Hematol 2007;82:615-24.
31. Patıroglu T, Eke Gungor H, Lazaroski S, Unal E. Chronic granulomatous disease with markedly elevated IgE levels mimicking hyperimmunoglobulin E syndrome. Acta Microbiol Immunol Hung 2013;60(2):155-62.
32. Inaba Y, Kanazawa N, Muraoka K, Yariyama A, Kawaguchi A, Kunimoto K, et al. Dupilumab Improves Pruritus in Netherton Syndrome: A Case Study. Children (Basel) 2022;24;9(3):310-8.
33. Zhang Q, Zhao YZ, Ma HH, Wang D, Zhang N, Li ZG, et al. Successful rescue of a lethal Griscelli syndrome type 2 presenting with neurological involvement and hemophagocytic lymphohistiocytosis: a case report. BMC Pediatr 2021;21:253-60.

34. Chovancova Z, Kralickova P, Pejchalova A, Bloomfield M, Nechvatalova J, Vlkova M, et al. Selective IgM Deficiency: Clinical and Laboratory Features of 17 Patients and a Review of the Literature. J Clin Immunol 2017;37(6):559-74.
35. Lawrence MG. Patterns of allergic sensitization in high IgE syndrome. Curr Allergy Asthma Rep. 2015;15(12):70.
36. Vuitton DA. The ambiguous role of immunity in echinococcosis: protection of the host or of the parasite? Acta Trop 2003;85(2):119-32.
37. Berciano FA, Crespo M, Bao CG, Alvarez FV. Serum levels of total IgE in non-allergic children. Allergy 1987;42:276-83.
38. Arinola OG. Serum Total IGE Levels in Healthy Children and Adults in Ibadan, Nigeria. Tanzania Medical Journal 2009;23(2):9-10.