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ORIGINAL ARTICLE

Is There a Clinical Significance of Very Low Serum Immunoglobulin E Level?

Serdar Al[1] · Suna Asilsoy[1] · Nevin Uzuner[1] · Gizem Atakul[1] · Özge Atay[1] · Özge Kangallı[1] · Işık Odaman Al[2] · Özkan Karaman[1]

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Abstract

Purpose High serum immunoglobulin (Ig) E levels are associated with allergies, parasitic infections, and some immune deficiencies; however, the potential effects and clinical implications of low IgE levels on the human immune system are not well-known. This study aims to determine the disorders accompanying very low IgE levels in children and adults.

Methods The patients whose IgE levels were determined between January 2015 and September 2020 were analyzed, and the patients with an IgE level < 2 IU/mL were included in this study. Demographic data, immunoglobulin levels, autoantibody results, and the diagnoses of the patients were noted from the electronic recording system of the hospital.

Result The IgE levels were measured in 34,809 patients (21,875 children, 12,934 adults), and 130 patients had IgE levels < 2 IU/mL. Fifty-seven patients were children (0.26%); 73 were adults (0.56%). There was a malignant disease in 34 (9 of them children) (26%), autoimmune diseases in 20 (3 of them children) (15.4%), and immunodeficiency in 17 (14 of them children) (13.1%) of the patients. The most common reasons were other diseases, immunodeficiency and malignancy in children, and malignancy, autoimmune disorders, and other diseases in the adults, in rank order. The IgE level did not show any correlation with the levels of other immunoglobulins.

Conclusion Although rare, a low IgE level has been shown to accompany malignancies, autoimmune disorders, and immune deficiencies. Patients with very low IgE levels should be carefully monitored for systemic disorders.

Keywords Adult · autoimmune diseases · child · immunoglobulin E · inborn error of immunity · neoplasms

Introduction

The term IgE was first used in 1968 associated with an immunoglobulin involved in allergic conditions [1]. High IgE level is well-known by clinicians and is associated with allergies, parasitic infestations, and less frequently, various immune deficiencies. A low IgE level is a warning for humoral immunodeficiencies, especially when the levels of other immunoglobulins are also low [2]. Isolated immunoglobulin (Ig) E deficiency is defined as a significantly low IgE level (< 2 international units/milliliter (IU/mL)) in a patient with normal levels of other immunoglobulins,

✉ Serdar Al
drserdaral@gmail.com

Suna Asilsoy
sunaasilsoy@hotmail.com

Nevin Uzuner
nuzuner@deu.edu.tr

Gizem Atakul
drgizematakul@gmail.com

Özge Atay
dr_ozge@hotmail.com

Özge Kangallı
ozgekangalli@gmail.com

Işık Odaman Al
dr.odamanal@gmail.com

Özkan Karaman
ozkan.karaman@deu.edu.tr

[1] Department of Pediatric Allergy and Clinical Immunology, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey

[2] Department of Pediatric Hematology and Oncology, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Izmir, Turkey

including IgG subclasses [3]. This is a laboratory finding that does not indicate a clinical disorder, and isolated IgE deficiency has not been included in international classifications for inborn error of immunity (IEI) disorders [4].

IgE deficiency (< 2 IU/ml) was determined in 3.3% of the US population. IgE deficiency has been observed in 75.6% (95% CI, 65.6–85.7%) of the patients with common variable immunodeficiency (CVID) and has been suggested as an inexpensive screening test for this condition [5].

In animal studies, it has been shown that IgE plays a role in tumor immunity [6]. In human studies, an inverse relationship has been found between atopy and various cancers (e.g., pancreas, brain, prostate, and colorectal) [7]. The European Academy of Allergy and Clinical Immunology (EAACI) has reported an association between very low IgE levels and an increased risk for malignancy and claimed that IgE level may be used as a new biomarker in the diagnosis of cancer[8, 9].

The studies on low IgE levels and autoimmunity mostly emphasized self-reactive IgE types of autoantibodies [10–12]. The pathogenesis of isolated low IgE levels has not been clarified. Defects in the immunoglobulin class-switch leading to the inability to produce IgE have not been clearly demonstrated [13]. However, activation-induced polymorphisms of cytidine deaminase genes in B lymphocytes have been blamed [14]. Although the absence of IgE-producing B lymphocytes was shown in patients with IgE deficiency, its mechanism has not yet been clarified [15]. It has been suggested that anti-epileptic drugs may cause hypogammaglobulinemia by affecting B cell maturation (i.e., Ig isotype switching), B cell number, and regulatory T lymphocytes [16].

The relation of IgE deficiency with diseases is not clear enough. In some studies, this has been associated with other immunoglobulin deficiencies, autoimmune disorders, reactive airway disease (rhinosinusitis, bronchitis, asthma), susceptibility to sinopulmonary infections, chronic fatigue, and arthralgia [8, 17]. The only study performed in children investigated its relationship with malignancy [18].

This study aimed to investigate the disorders associated with very low IgE levels and the relationship of the IgE levels with the levels of other immunoglobulins in adults and children.

Methods

The patients who were admitted to Dokuz Eylul University Faculty of Medicine (DEU) Hospital between January 2015 and September 2020 and had an immunoglobulin E (IgE) level < 2 IU/mL were analyzed. The data were obtained retrospectively from the hospital medical recording center and checked by two independent investigators. The patients' demographic data, including age and gender as well as the levels of IgE and other immunoglobulins (Ig) IgA, IgG, and IgM; the presence of autoantibodies, including anti-nuclear-antibody (ANA) and anti-double stranded DNA antibodies (anti dsDNA); extractable nuclear antigens (ENA panel); anti-thyroid peroxidase (Anti TPO); and anti-thyroglobulin (Anti TG), were recorded. The international disease classification (ICD-10) diagnoses of the patients were classified into groups, including immunodeficiencies, malignancy, autoimmune disorders, atopic disorders, infections, and others, after examining the details of their archived files. Hematological and solid malignant tumors were included in the malignancy group. Vasculitis disorders, including sarcoidosis, scleroderma, rheumatoid arthritis, systemic lupus, Hashimoto thyroiditis, type 1 diabetes mellitus, and autoimmune hemolytic anemia, were included in the autoimmunity group. The patients diagnosed with asthma, allergic rhinitis, eczema, anaphylaxis, food allergy, and chronic urticaria were included in the group of atopic disorders. The disorders other than the aforementioned ones (e.g., neurological disorders, congenital heart disease, kidney diseases) were included in the other diseases group. Low-normal-high levels of the immunoglobulins were determined in relation to the patients' age, considering reference ranges for children and adults [19]. The values below − 2 SDS according to reference ranges were accepted as low immunoglobulin levels. The data were recorded on a standard registration form.

Statistics

The data were analyzed using IBM SPSS Statistics 22.0 (IBM Corp. Armonk, New York, USA) package program. The descriptive data were presented as the unit numbers (n), percentage (%), and mean ± standard deviation ($\bar{x} \pm SD$), and the data that did not conform to normal distribution were given as median and minimum–maximum values. Inter-group comparisons were made with one-way analysis of variance for variables with normal distributions and Kruskal–Wallis analysis for variables without normal distributions. The multiple comparison tests used were Tukey HSD for normally distributed variables and Dunn–Bonferroni and Welch's tests for non-normally distributed variables. Logistic regression test was used as a multivariate analysis to calculate probability ratios (ORs) and 95% confidence intervals (95% CI). Spearman correlation test was used to calculate the correlation among the immunoglobulin levels. Dependency of the categorical variables was analyzed using chi-square, Yates correction, and Fisher's exact tests. A p value < 0.05 was considered statistically significant.

Results

Between January 2015 and September 2020, 34,809 patients were identified who had their IgE levels measured; 21,875 of them were children (< 18 years of age), and 12,934 of them were adults (≥ 18 years of age). In 130 (0.37%) of these patients, the IgE level was < 2 IU/mL; 57 (43.8%) were children, and 73 (56.2%) were adults. The IgG, IgA, and IgM levels were analyzed after exclusion of extreme values of two cases diagnosed with multiple myeloma (Table 1). The disease groups with accompanying low IgE levels in children and adults are presented in Fig. 1.

In the analysis of the adults and the children in relation to their diagnoses, it was seen that malignancy (34.3%), autoimmune diseases (23.3%), and other diseases (16.4%) were the most frequent in adults, while other causes (26.3%), IEI (26.3%), and malignancy (14%) were the most frequent disease groups in children. The number of patients with comorbidities involving more than one different system was 14 (10.8%). There was no significant difference between the group with and without more than one comorbidity concerning IgE ($p = 0.206$).

The data of cases with malignancy are summarized in Table 2.

Autoimmune disorders were evident in 17 (23.3%) adults and three (5.3%) children. Autoantibodies were measured in 59 (45.4%) patients, and 17 (24%) of them (two children, 15 adults) were positive for autoantibodies. Of the patients with autoantibodies, 11 (65%) had autoimmune disease, four (23.5%) had malignancy, and two (11.5%) had other causes. Autoimmune disorders and positive autoantibodies ($p < 0.001$, 95% CI, 2.945–41.084) were correlated with female gender ($p = 0.010$, $\chi 2 = 6.653$, $SD = 1$). In three children diagnosed with autoimmune disorders, the diagnoses were SLE + lupus nephritis, IBD + epilepsy, and autoinflammatory syndrome.

The characteristics of the adult patients are summarized in Table 3.

Inborn error of immunity was detected in 15 (26.3%) children and three (4.1%) adults. CVID was observed in two, and ataxia-telangiectasia was seen in one adult patient. Eight (14%) children had humoral IEI, three (5.2%) had severe combined immunodeficiency, and four had other IEIs (ataxia-telangiectasia in two, DiGeorge syndrome, congenital neutropenia). Lymphoma developed in one of the patients diagnosed as ataxia-telangiectasia.

Atopic disorders were detected in 18 (13.8%) patients; seven of them were children. There was recurrent wheezing in four, asthma in two, and atopic dermatitis in one of the pediatric cases. Among adults, asthma and/or chronic obstructive pulmonary disease was evident in six, chronic urticaria in three, and atopic dermatitis in two cases. Some of the cases with chronic urticaria (two cases) had the diagnosis of Hashimoto thyroiditis and were included in the autoimmunity group, while the cases with idiopathic chronic urticaria (three cases) were included in the atopic disorder group.

Various infections accompanied low IgE level in seven (5.4%) patients. Complicated pneumonia, chronic otitis media, recurrent adenotonsillitis, and pertussis were detected in four children, while bronchiectasis, recurrent otitis, and skin infection (erysipelas) were detected in adults. The patients with infection and detected IEIs were included in the IEI group.

Neurological disorders were identified in seven (12.3%) of 15 children, who were classified in the other diseases' group. Seven of them had resistant epilepsy and were on multiple anti-epileptics. Four (7%) had congenital heart disease (aortic arch anomalies), three (5.3%) had genetic syndrome (two of them had Down syndrome and one of them had cri du chat syndrome), and one (5%) had metabolic disorder (cystic fibrosis). Of 12 adult patients, four (5.5%) had a chronic renal failure (two with kidney transplantation), four (5.5%) diabetes mellitus, three (4.1%) aplastic anemia, and one notalgia paresthetica. No pathologies were determined in seven (5.4%) cases; five of them were children.

The IgE level was lower in those with at least one low level of antibody accompanying low IgE (low IgE + at least one antibody low median/range IgE, 1.02/1.99 IU/ml; low IgE + normal antibodies median/range IgE, 1.25/1.99 IU/ml, $p = 0.018$). Low IgE level was found in the malignancy group, while low antibody levels were most prominently in

Table 1 Demographic characteristics and immunoglobulin levels of patients with IgE < 2 IU/ml

	Children ($n = 57$, 0.26%)	Adults ($n = 73$, 0.56%)
Median (range) year	6 (16)	60 (70)
Female (n, %)	26 (45.6)	46 (63)
Male/female	1.19:1	0.59:1
IgG (median range) (mg/dL)	514.5 (1153)	1010 (2582)
IgA (median range) (mg/dL)	43 (447)	145 (586)
IgM (median range) (mg/dL)	53 (245)	84 (335)
IgE (median range) (mg/dL)	1.18 (1.74)	1.23 (1.99)

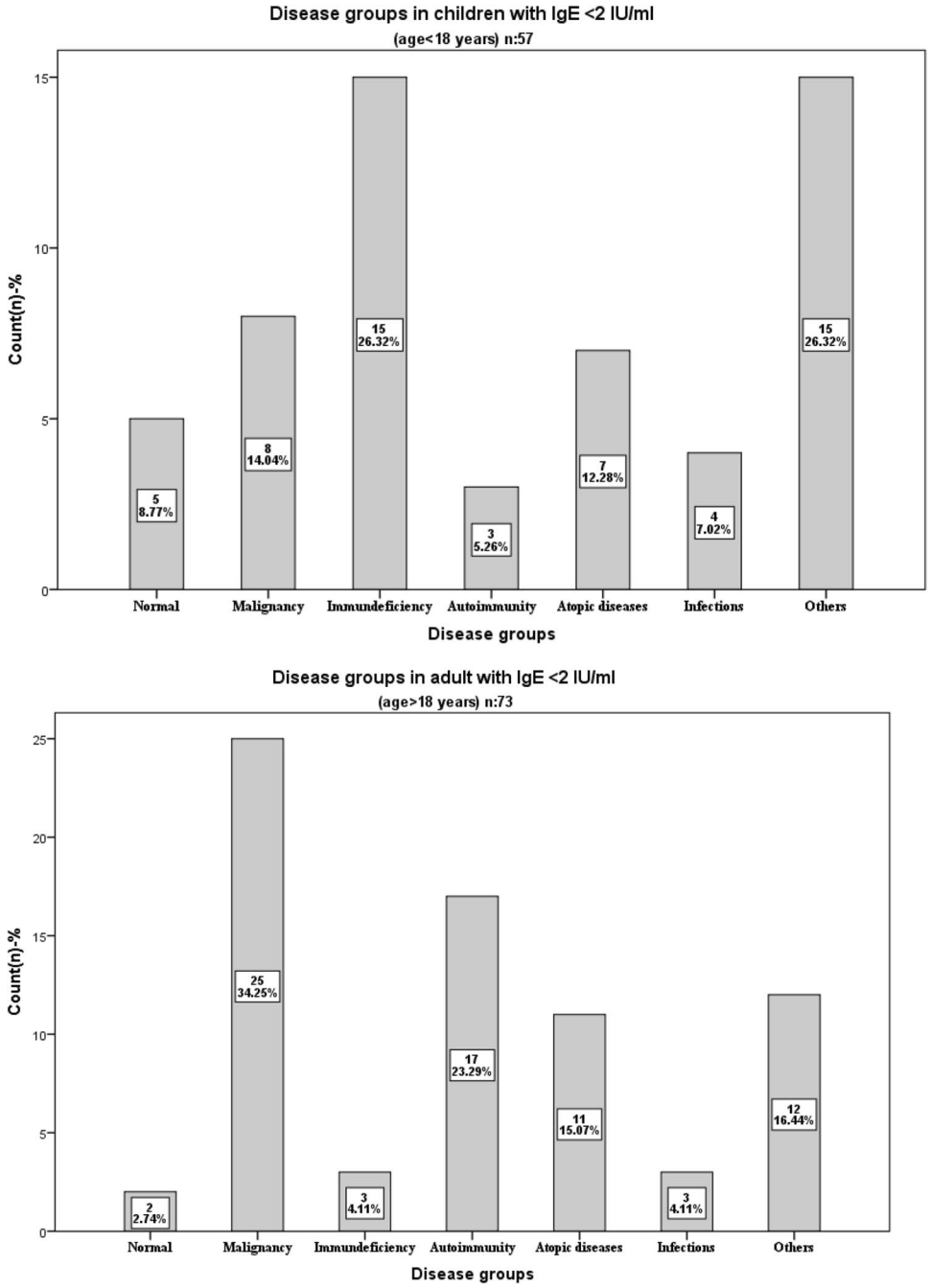

Fig. 1 The distribution of the children and the adults with an IgE level < 2 IU/mL by the disease groups

the IEI group. IgE level was not correlated with the levels of other immunoglobulins. IgG and IgA levels were strongly correlated ($rho = 0.610$, $p < 0.001$), while IgG and IgM ($rho = 0.474$, $p < 0.001$) as well as IgA and IgM levels ($rho = 0.435$, $p < 0.001$) were moderately correlated. These results indicate significant correlations among IgG, IgA, and IgM levels, however, not with very low levels of IgE (Fig. 2).

Genders and the diagnosis groups were not correlated ($\chi 2 = 8.712$, $SD = 6$, $p = 0.190$). When the diagnoses of all patients with low IgE levels were analyzed in relation to their ages, the mean age of patients diagnosed with immunodeficiency was smaller ($p < 0.01$) (Fig. 3 shows the age distribution of the patients in relation to the diagnoses).

Discussion

Recently, low IgE level has been a remarkable subject, and many investigations have been conducted on it. In our study, we aimed to identify the disease groups that might be associated with low IgE levels in children and adults. Thus, the patients whose IgE levels were determined in the

Table 2 The data of the patients with malignancy

	Children (*n*:8)	Adults(*n*:25)
Male *n* (%)	4 (50%)	9 (36%)
Male:female	1:1	0.56:1
Age (mean ± SD) year	9.25 ± 5.3	67 ± 17.4
Low IgG[1] (%)	4/7 (57.1%)	6/23 (26.1%)
Low IgA[1] (%)	2/7 (28.6%)	7/22 (31.8%)
Low IgM[1] (%)	4/7 (57.1%)	3/18 (16.7%)
IgE (mg/dL) mean ± SD	1.32 ± 0.43	1.08 ± 0.56
Malignancy *n* (%)		
Hematological (*n*:30)	3 (37.5%)	17 (68%)
Solid Tumor (*n*:15)	5 (62.5%)	8 (32%)
Hematological	Lymphoma (3)[2] - - -	Lymphoma (5)[3] KLL(6)[4] Multiple myeloma (5) MPN(1)
Solid Tumor	Neuroblastoma (2) Ewing sarcoma (1) Hepatoblastoma (1) Ependymoma (1)	Colon Ca (2) Breast Ca (2) Pancreatic Ca (1) Renal Ca (1) Thyroid papillary Ca (1) Neuro-endocrine tumor (1)

[1]Low immunoglobulin refers to < (-) 2 SDS

[2]In addition, lymphoma was developed in a patient with ataxia-telangiectasia, who was in the group of IEIs not evaluated here

[3]Bladder plasmacytoma developed in one patient during the follow-up period

[4]Sarcomatoid tumor developed in one patient

MPN, chronic myeloproliferative neoplasms; *CLL*, chronic lymphocytic leukemia; *ALL*, acute lymphocytic leukemia; *Ca*, cancer

last 5 years were screened. Among these, the patients with low IgE levels were analyzed for their diagnoses. Malignant and autoimmune disorders were detected at high rates. Low IgE levels did not show any correlation with the levels of other immunoglobulins. Autoimmune disorders were more frequent in patients who had autoantibodies and in females. The results of this study suggest that the role of IgE in the immune system, and its functions in malignancy and autoimmunity, should be further clarified, and IgE deficiency should be taken seriously when encountered.

An IgE level < 2 IU/mL is defined as IgE deficiency. Its prevalence has been determined as 2.4% in the US population over the age of 6 years [20]. This prevalence was reported as 1.95% in a meta-analysis analyzing many cohorts [5]. The patients included in our study were those whose IgE levels were measured for any reason in our hospital. Therefore, our results do not present the prevalence in our society. In our study, an IgE level < 2 IU/mL was determined in 0.37% of the patients who had IgE level measurements.

The annual cancer diagnosis rate in Turkey is 0.28% [21]. The relationship between IgE level and cancer has been investigated in various studies. An inversely proportional relationship was shown between allergic sensitization and cancer development, high IgE levels were associated with a lower risk of multiple myeloma and chronic lymphoid leukemia (CLL), and patients diagnosed with glioma and multiple myeloma had a longer life expectancy if their total IgE levels were high [22–27]. The relationship between IgE levels and cancer may indicate the role of T helper 2-mediated immune response in the development or control of some cancers. The studies conducted in line with this hypothesis have found that mice injected with breast cancer cells fight the tumor better and have a longer life span if they had a higher IgE level spontaneously [6]. Again, it was determined that tumor spread increased in mice whose IgE responses were destroyed, and tumor growth was well-controlled in mice with strong IgE responses [28]. Recently, many chimeric IgE studies have been conducted in cancer treatment [29]

In our study, the relationship between malignancy and IgE was inversely proportional. The association of cancer (predominantly hematological cancers) and very low IgE

Table 3 The distribution of the adults with autoimmune disorders

Diseases	Adult (*n*:17) *n* (%)	Comorbid conditions
Systemic sclerosis	3 (17.6%)	Pulmonary involvement in one case
Hashimoto thyroiditis	3 (17.6%)	Chronic urticaria in two cases, diabetes, and interstitial lung disease in one case
Systemic lupus erythematosus	3 (17.6%)	
Interstitial lung disease	2 (11.7%)	
Psoriasis	1 (5.8%)	Spondyloarthropathy
Inflammatory bowel disease	1 (5.8%)	Spondyloarthropathy
Sarcoidosis	1 (5.8%)	
Sjogren's syndrome	1 (5.8%)	Interstitial lung disease
Ankylosing spondylitis	1 (5.8%)	Chronic renal failure + kidney transplantation
Multiple sclerosis	1 (5.8%)	

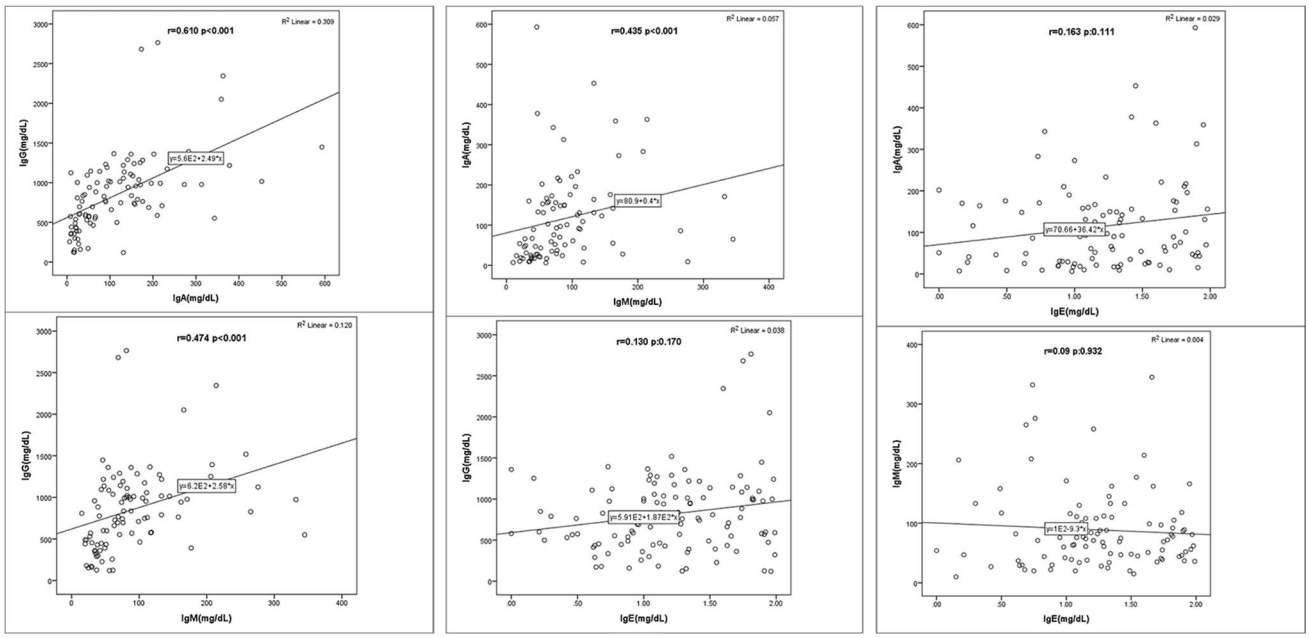

Fig. 2 The graph showing the correlations of immunoglobulins

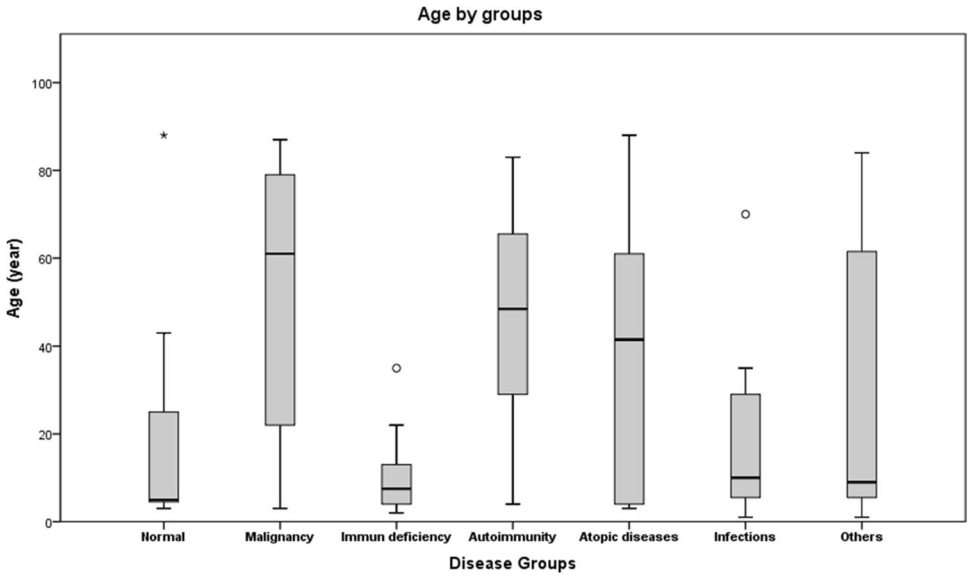

Fig. 3 Age distribution of the disease groups

levels appears to occur even in the absence of a known immunodeficiency. It is not very well-known whether IgE deficiency is a predisposing factor for cancer or a sign of cancer before its development due to a modulation disorder in the immune system. However, our study suggests that low IgE levels may be considered as a red flag, and the cases may be followed up closely concerning cancer development even if the clinical picture is normal at that time.

Information on autoantibody seroprevalence in the healthy Turkish population is not sufficient. In a study conducted with an adult group, the seroprevalence of ANA at 1/80 titer was 14.93% [19]. We think that determining this rate as 24% in our patients with autoantibodies was because the tests were planned in patients with clinical autoimmune disease. In our study, autoimmune disorders were determined in 15.4% of the cases. As expected, this was associated with autoantibody positivity, female gender. Mainly, connective tissue disorders were evident. In the study of Smith et al. [17], the incidence of autoimmune disorders was significantly higher in patients with low IgE levels compared to the control group. It is generally thought that there is an inversely proportional relationship between allergy and

autoimmunity. It has been suggested that this relationship is T helper-induced; the Th2-mediated atopic disorders are less common in patients with Th1-mediated autoimmunity and may prevent the development of autoimmunity or alleviate the clinical symptoms in allergic disorders where Th2 inflammation is more prominent [30, 31]. In addition, it has been claimed that gain-of-function mutation in the STAT3 is an immune deficiency accompanied by autoimmunity and recurrent infections. IgE level was < 2 IU/mL in the ones with this mutation, and it was reported that it could be used as a screening test [32]. In another study, it was suggested that it could not be used as a screening test since its sensitivity and specificity were low [33]. In the literature, the studies on IgE and autoimmunity are mostly on developing self-reactive IgE type of autoantibodies in autoimmune disorders [12, 34, 35]. The cases in the IEI group mostly had humoral IEIs. It is an expected finding that all immunoglobulins will be affected in humoral IEI. IgE deficiency is frequently seen in CVID and correlates with low levels of other immunoglobulins [5]. Other causes of humoral IEI, ataxia-telangiectasia, and combined immunodeficiencies may also lead to IgE deficiency [4].

Since IgE is a mucosal immunoglobulin, it may play a role in the immune response in case of exposure to exogenous antigens. IgE is not only mucosal but also systemic immunoglobulin and plays a role in the pathophysiology of diseases such as anaphylaxis. It has been shown that IgE production is insufficient in mice with experimental lymphotoxin deficiency; these mice have more airway inflammation and bronchial hyperactivity, but the inflammation is Th1 type [36]. In our study, atopic diseases were determined in 18 (13.8%) patients, and airway disease was more common.

It has been determined that upper respiratory tract infections are more common in patients with very low IgE levels compared to patients with normal and high IgE levels [17, 37]. In our study, mainly sinopulmonary infections were determined. No parasitic infections were found. In the literature, it has been reported that sinopulmonary infections are frequently encountered in cases with very low IgE levels [38, 39]. The role of IgE in mucosal defense may explain this condition.

In our study, the other diseases group constituted 26.3% of the child patients. The most common disorders in this group were neurological diseases, and resistant epilepsies were the most frequently encountered disorders. In these cases, IgE deficiency may often be associated with the use of anti-epileptics. Anti-epileptics have been shown to reduce immunoglobulin levels [40, 41]. Another reason was congenital heart anomalies requiring surgery. Most of our patients had aortic arch anomalies. The genetic disease most commonly associated with aortic arch anomalies is DiGeorge syndrome, which also causes low immunoglobulin levels [42]. In these patients, low IgE levels may be secondary to unspecified complete or incomplete DiGeorge syndrome or intervention to the thymus during surgery. In adults, chronic renal failure, complicated diabetes, and aplastic anemia were the most common disorders. Medications used for chronic renal failure, malnutrition, and following renal transplantation may cause hypogammaglobulinemia [41].

During longer follow-up, IEI patients commonly develop malignancies and autoimmune diseases [4]. While in children the most common diseases associated with low IgE were IEI, in adult patients, low IgE was most frequently associated with malignancies and autoimmune diseases. The identified IEI in our study included mostly well-known antibody deficiencies and monogenic defects. We cannot exclude unidentified, novel, or ultrarare IEI in adults with low IgE, malignancies, and/or autoimmunity. Further, larger-scale, well-controlled studies are needed to clarify these questions.

The main limitations of this study are its retrospective design and the absence of a control group, which has led to failure in the standardization. The IgE measurements of the cases were made predominantly before the diagnosis and during the diagnostic procedures. However, test results obtained after diagnosis were also available. IgG, IgA, and IgM levels and autoantibodies were not measured in every patient, which caused data loss. Both IgE and other tests were ordered as the clinicians decided, not according to a standard algorithm. Because of that, the IgE level was not measured in every person admitted to the hospital. In addition, we could not evaluate the effects of low IgE level on the course of the diseases due to the retrospective nature of this study.

Another limitation in this study was the lack of the control group, hence not designing this study as a randomized controlled study, and lack of comparison with the groups with normal and high IgE levels. However, while planning this study, we set out to investigate how very low IgE levels are reflected in the clinical picture. Therefore, we wanted to analyze only cases with IgE deficiency.

That the data were obtained from a limited sample group and the lack of any information on the prevalence of IgE deficiency in our country were among the limitations of our study. We hope that our study will guide further studies on the role of IgE in the pathogenesis of diseases and the studies on targeted therapies.

Conclusions

Very low IgE levels may accompany critical systemic disorders. Prospective studies are needed to establish a cause-and-effect relationship and whether a very low IgE level plays a role in the pathophysiology of associated disorders. When encountered with very low IgE levels, it will be beneficial

for clinicians to keep systemic disorders in mind and conduct investigations in line with the patient's complaints.

Abbreviations Ig: Immunoglobulin; IU/mL: International units milliliter; USA: United States of America; CVID: Common variable immunodeficiency; EAACI: European Academy of Allergy and Clinical Immunology; DEU: Dokuz Eylul University Faculty of Medicine; ANA: Anti-nuclear antibody; Anti dsDNA: Anti-double stranded deoxyribonucleic acid antibodies; ENA: Extractable nuclear antigens; Anti TPO: Anti-thyroid peroxidase; Anti TG: Anti-thyroglobulin; ICD-10: The International Disease Classification 10; IEI: Inborn error of immunity; CLL: Chronic lymphoid leukemia; SLE: Systemic lupus erythematosus

Author Contribution All authors contributed to this study's conception and design. Material preparation, data collection, and analysis were performed by Serdar Al, Gizem Atakul, Özge Atay, Özge Kangallı, Işık Odaman Al, Suna Asilsoy, Nevin Uzuner, and Özkan Karaman. The first draft of the manuscript was written by Serdar Al and Suna Asilsoy, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of Dokuz Eylul University Non-Interventional Studies Ethics Committee (Decision No: 2020/29–47).

Consent to Participate Not applicable.

Consent for Publication The authors of this manuscript attest that they have all reviewed this manuscript and have contributed in a substantively and intellectually manner to the work described.

Conflict of Interest The authors declare no competing interests.

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