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The spectrum of inborn errors of immunity: a single tertiary center retrospective study in Alborz, Iran

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Key words

Inborn errors of immunity; clinical features; immune system; demographic characteristics; heterogeneous disorders.

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Impact statement

The most common known immunodeficiency disease in the present study was immunoglobulin A deficiency (IgAD), severe combined immunodeficiency (SCID) and common variable immune deficiency (CVID).

Summary

Background. *Inborn errors of immunity (IEIs) are a group of heterogeneous disorders with inherited faults in the immune system that increase susceptibility to infections, malignancies, lymphoproliferation, and autoimmune/autoinflammatory disorders.* ***Methods.*** *We retrospectively studied the demographic characteristics, clinical features, and immunological profiles of the 90 IEIs patients, who were diagnosed and classified according to the European Society for Immunodeficiencies (ESID) and International Union of Immunological Societies (IUIS) criteria from July 2010 to June 2021. The study was carried out in the Non-communicable Diseases Research Center, Imam Ali Hospital, Alborz, Iran.* ***Results.*** *Within a period of 11 years, 53 (58.9%) males and 37 (41.1%) females were diagnosed and followed-up for 20 IEI disorders. The median (IQR) age of onset, age of clinical diagnosis and diagnostic delay was 0.7 (0.08-2.0), 3.18 (1.0-8.0) and 1.5 (0.17-5.0) years, respectively. Twelve patients (36.4%) had a positive family history of IEI, and the majority of patients (84.5%) had recurrent infections. Pneumonia (51.7%) was the most common clinical manifestation among IEI patients, followed by skin complications (46.2%). The most frequently diagnosed IEI was immunoglobulin A deficiency (IgAD) (14.4%) and severe combined immunodeficiency (SCID) (11.1%). Predominantly antibody deficiencies group (36.7%) was the most common category, followed by combined immunodeficiencies with associated or syndromic features group (27.8%).* ***Conclusions.*** *IEIs have different patterns within populations with high consanguinity. There is a need to searching for underlying genetic and epigenetic factors in most common IEIs in Alborz.*

Introduction

Inborn errors of immunity (IEIs) is considered a heterogeneous group of more than 400 inherited disorders, leading to qualitative or quantitative defects in immune system components (1, 2). Patients with IEI are generally prone to recurrent and persistent or unusual serious infections and some have a tendency to immune dysregulation (3). They have a widespread phenotype with often high rates of mortality and morbidity, making the diagnosis and treatment challenging (4). IEI clinical manifestations include, but are not limited to, recurrent infections, autoimmune/inflammatory diseases, enteropathy, failure to thrive, allergy, lymphoproliferation and/or malignancy (5). During the last decade, recent progress in genetic research and immunological finding has allowed a greater understanding of pathomechanisms underlying IEIs (6). On the other hand, the development and use of diagnostic techniques, especially flow cytometry analysis and next-generation sequencing, significantly have helped facilitate the diagnosis of IEIs (7). However, general practitioners/pediatricians as the first encounterers may not be able to recognize patients suspected of IEI due to the lack of training and awareness, which is the main reason for delayed diagnosis or misdiagnosis and inadequate treatment, which leads to unfavorable consequences (8, 9).

The incidence of IEI disorders, ranges from 1:500 to 1:1,000,000, depending on the specific primary genetic defect and geographical region (10, 11). The overall predicted prevalence of IEIs is almost 1 in 1200 live births except for immunoglobulin A (IgA) deficiency, which is more common in the general population (12, 13). However, the prevalence of IEIs are supposed to be more than the world's average due to the high consanguinity rate in Iran (10).

This study aimed to report the distribution, clinical presentations, and immunologic features of 90 IEI patients living in Alborz province, Iran.

Materials and methods

Data collection

This longitudinal study was carried out in the Non-communicable Diseases Research Center, Imam Ali Hospital, Alborz, Iran. All patients with IEI, diagnosed during the period from July 2010 to June 2021, were included in the study. A total of 90 patients were included for classification and investigation based on updated diagnostic guidelines confirmed by the European Society for Immunodeficiencies (ESID) working party (14). In addition, the gathered information was entered into the data form and divided into five sections: laboratory and molecular findings, clinical manifestations, sociodemographic data, and current life status. Immunodeficiencies secondary to other conditions (*e.g.*, human immunodeficiency virus infection, malnutrition and medical treatment) were excluded as well. The study was approved by the Ethics Committee of the Alborz University of Medical Sciences (Approval code: IR.ABZUMS.REC.1399.241).

Evaluation sheet

For documentation, an evaluation sheet was developed to contain all patients' demographic data such as age, gender, age at onset of symptoms, age at diagnosis, delay of diagnosis, parental consanguinity, family history of IEI, dead or alive status and clinical manifestations. Laboratory investigations were performed using standard techniques and included complete blood count, peripheral blood lymphocyte subsets including the basic panel of T-cell subsets (CD3, CD4, CD8), B-cell (CD19, CD20), and natural killer cell (CD56/16) − assessed using flow cytometry analysis −, and measurement of serum immunoglobulins (IgG, IgA, IgM, and IgE) level − assessed using nephelometry and enzyme-linked immunosorbent assay (ELISA). If required, Nitroblue tetrazolium test (NBT), measurement of serum alpha-fetoprotein (AFP), assessment of the expression of CD18/CD11 on neutrophils by flow cytometry, complement hemolytic activity (CH50), anti-tetanus IgG, anti-diphtheria IgG, and also anti-pneumococcal antibody titer were performed. In addition, patients with incomplete data or those who did not meet the ESID criteria were excluded. Medical data were obtained after receiving written informed consent from all patients or/and their surrogates.

Statistical analysis

Information were gathered in an Excel database and were converted for analysis using the SPSS statistical software package version 25.0 (IBM corporation, Chicago, IL, USA). The Shapiro-Wilk test was used to validate the assumption of normality for a variable, and the nonparametric or parametric tests were carried out according to the normality supposal. Frequency and percentages were reported for qualitative variables and median (interquartile range, IQR) for quantitative variables. Fisher's exact test and $\chi 2$ tests were used for 2×2 comparisons of categorical variables. To compare numerical variables, the nonparametric Mann-Whitney U test was used. A P-value < 0.05 was considered statistically significant.

Results

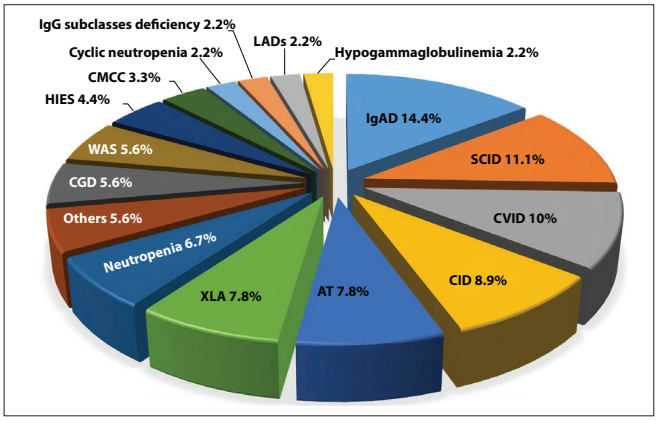
Epidemiologic characteristics of IEI patients

Totally, 90 patients with 20 types of IEIs diagnosed from July 2010 to June 2021 were enrolled in the study (**figure 1**). As shown in **figure 1**, immunoglobulin A deficiency (IgAD) was the most common IEI (13 patients (14.4%)), followed by severe combined immune deficiency (SCID) and common variable immune deficiency (CVID) in 10 (11.1%) and 9 (10.0%) patients, respectively. The median age of patients at the time of the study was 13.0 years (IQR:

4.0-24.0 years, varying from 0.2 to 46 years). The median (IQR) age of onset, age of clinical diagnosis and diagnostic delay was 0.7 (0.08-2.0), 3.18 (1.0-8.0) and 1.5 (0.17-5.0) years, respectively. The male/female ratio was approximately 1.4:1 (53 (58.9%) male and 37 (41.1%) female). At the time of the study, 54 (78.3%) patients were alive and 15 (21.7%) patients were deceased.

The detailed demographical data is summarized in **table I**. The highest age of clinical diagnosis belonged to CVID patients (median (IQR):11.96 (4.56-21.29) years) and the longest delay in diagnosis was observed in hyper IgE syndrome (HIES) patients (median (IQR): 7.0 (7.0-7.0) years). Also, the lowest delay in diagnosis and the shortest duration from diagnosis to death were found in SCID patients with a median (IQR) 0.1 (0.09-1.0) and 0.94 (0.2-18.35) years, respectively. The median (IQR) age of CVID and CID patients (23.0 (15.75-30.25) and 2.0 (0.55-3.87) years, respectively), were the highest and the lowest age at the time of the study. The detailed patient's demographical data in the ten most common IEI phenotypes are represented in **table II**. According to the ten categories of International Union of Immunological Societies criteria (IUIS), most of the patients were in the predominantly antibody deficiencies group (n = 33, 36.7%), followed by combined immunodeficiencies with associated or syndromic features (n = 25, 27.8%) and congenital defects of phagocyte number and function (n = 15, 16.7%) groups. **Table III** shows the detailed distribution of reported clinical diagnoses in the ten categories of IUIS classification. Among ninety registered patients, 25 patients (27.8%) had confirmed molecular diagnosis.

***Figure 1** - The distribution of patients with IEI diagnosis.*



The most common clinically diagnosed IEIs were IgAD and SCID. Others include HIgM, ICF syndrome, hereditary angioedema, ALPS-like, and complement deficiency. The frequency of each of them is approximately 1.1% (one person). CVID: common variable immune deficiency; SCID: severe combined immune deficiency; AT: ataxia-telangiectasia; XLA: x-linked agammaglobulinemia; IgAD: immunoglobulin A deficiency; CGD: chronic granulomatous disease; HIES: hyper-IgE syndromes; WAS: Wiskott-Aldrich syndrome; CMCC: chronic mucocutaneous candidiasis; CID: combined immune deficiency; LAD: leukocyte adhesions deficiency syndrome; HIgM: hyper immunoglobulin M; ALPS-like: autoimmune lymphoproliferative syndrome Like; ICF: immunodeficiency centromeric region instability facial anomalies syndrome.

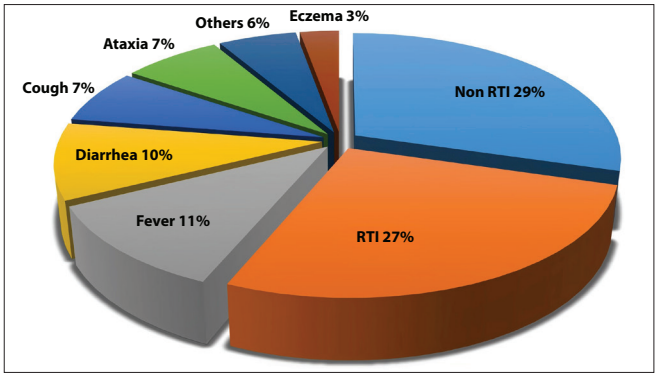
Clinical spectrum of IEI patients

In our study, 12 of 33 patients with available data (36.4%) had a positive family history of IEI. The history of infectious complications was reported in 60 patients (84.5%). Twenty-three types of clinical manifestations were reported as the first clinical presentation of IEI patients. Respiratory tract infections (RTI) (27.0%), including pneumonia, sinusitis, sinopulmonary infections, otitis media, common cold, recurrent pharyngitis, and non-respiratory tract infections (nRTI) (29.0%), including urinary tract infections, skin infections, gastrointestinal infections, BCGosis, oral candidiasis, eczema and arthritis, were the most common first presentation in IEI patients (**figure 2**).

As shown in **table IV**, the most reported clinical manifestations among patients were pneumonia (51.7%), skin complications (46.2%) (include dermatitis, psoriasis, eczema and vitiligo), and otitis media (41.8%). In patients with IgAD and SCID, as the most frequent clinical diagnosis, the most common presentation was pneumonia (66.7% and 83.3%, respectively).

Nineteen cases had a history of autoimmunity and ten of them had polyautoimmunity. Most of the patients with autoimmunity had an ultimate diagnosis of IgAD (36.8%), CVID (26.3%), or ataxia-telangiectasia (10.5%). The most common autoimmune disorders were hypothyroidism and Insulin-dependent diabetes mellitus (IDDM), each was found in seven people (7.8%).

***Figure 2** - The first clinical presentation in patients with IEIs.*



The most common first presentation in IEI patients was Non RTI (29.0%) and RTI (27.0%). Others include: failure to thrive, bleeding, limb swelling and periorbital edema, each found in one person (1.5%). RTI includes: pneumonia, sinusitis, sinopulmonary infections, otitis media, cold and recurrent pharyngitis. Non RTI includes: urinary tract infections, skin infections, gastrointestinal infections, arthritis, BCGosis, oral candidisis and eczema. RTI: respiratory tract infection.

Table I *- Demographic data of patients in most categories of inborn errors of immunity.*

Parameters	Total (n = 90)	Predominantly antibody deficiencies (n = 33)	Combined immunodeficiencies with associated or syndromic features (n = 25)	Congenital defects of phagocyte number, function, or both (n = 15)	Immunodeficiencies affecting cellular and humoral immunity (n = 11)	P-value
Age, y, median (IQR)	13.0 (4.0-24.0)	21.0 (8.0-27.0)	7.0 (2.75-16.25)	9.0 (5.5-23.25)	2.0 (0.5-16.75)	**0.014***
Sex ratio, M/F	53/37	25/8	13/12	7/8	5/6	0.109
Consanguinity, %	45 (59.2)	12 (46.2)	9 (40.9)	10 (76.9)	10 (90.9)	**0.014***
Dead/Alive (%)	15/54 (21.7)	9/15 (37.5)	1/18 (5.3)	0/12 (0)	5/5 (50)	**0.003***
Age at onset, y, median (IQR)	0.7 (0.08-2.0)	1.08 (0.52-3.1)	0.25 (0.0-1.37)	0.0 (0.0-2.0)	0.3 (0.11-1.05)	**0.043***
Age at clinical diagnosis, y, median (IQR)	3.18 (1.0-8.0)	4.0 (1.51-12.94)	2.0 (0.5-7.0)	5.0 (1.75-6.12)	0.55 (0.18-2.75)	**0.031***
Delay in diagnosis, y, median (IQR)	1.50 (0.17-5.0)	2.35 (0.44-5.07)	1.0 (0.16-6.5)	2.5 (0.37-5.37)	0.17 (0.09-1.87)	0.288
Course of disease, y, median (IQR)	12.11 (4.97-22.25)	13.95 (8.0-21.81)	6.5 (3.73-21.25)	15.5 (7.39-26.0)	1.5 (0.2-16.8)	0.125

M: Male; F: Female; N: Count; Y: Year; the median is shown with 25th and 75th percentiles; *P-value is statistically significant < 0.05.

Table II *- Demographic data of patients in the ten most common inborn errors of immunity.*

Category	No. of cases	Age, y, median (IQR)	Sex ratio, M/F	Consanguinity (%)	Age at onset, y, median (IQR)	Age at diagnosis, y, median (IQR)	Delay in diagnosis, y, median (IQR)	Course of the disease, y, median (IQR)
IgAD	13	12.0 (8.0-23.0)	9/4	37.5	0.29 (0.0-3.02)	3.09 (0.79-5.0)	1.7 (0.09-5.0))	11.4 (8.0-17.45)
SCID	10	2.0 (0.5-18.0)	4/6	90	0.3 (0.11-0.75)	0.4 (0.16-1.64)	0.1 (0.09-1.0)	0.94 (0.2-18.35)
CVID	9	23.0 (15.75-30.25)	5/4	75	4.5 (2.0-14.69)	11.96 (4.56-21.29)	1.96 (0.43-7.06)	14.45 (4.25-18.75)
CID	8	2.0 (0.55-3.87)	4/4	50	0.18 (0.04-0.80)	0.75 (0.16-N/A)	N/A	3.34 (2.0-N/A)
AT	7	13.0 (10.5-27.0)	1/6	66.7	1.0 (0.3-2.0)	4.0 (2.0-9.0)	4.0 (0.2-8.5)	13.0 (9.0-25.85)
XLA	7	22.0 (4.0-26.0)	7/0	28.6	0.7 (0.6-1.0)	3.0 (1.35-5.80)	2.3 (1.1-5.1)	21.75 (3.4-25.3)
Neutropenia	6	8.0 (2.1-22.5)	2/4	100	0.0 (0.0-3.0)	4.0 (2.25-5.75)	2.5 (1.25-4.5)	8.0 (8.0-N/A)
CGD	5	16.5 (7.0-23.7)	1/4	75	0.0 (0.0-N/A)	5.75 (5.0-12.87)	6.5 (0.0-N/A)	23.0 (5.58-N/A)
WAS	5	5.0 (3.5-25.0)	5/0	20	0.05 (0.0-2.27)	0.65 (0.19-5.50)	0.60 (0.17-3.25)	4.95 (2.72-28.25)
HIES	4	28.0 (8.0-N/A)	2/2	0	0.0 (0.0-0.0)	7.0 (7.0-7.0)	7.0 (7.0-7.0)	N/A

M: Male; F: Female; Y: Year; the median is shown with 25th and 75th percentiles; IgAD: immunoglobulin A deficiency; SCID: severe combined immune deficiency; CVID: common variable immune deficiency; CID: combined immune deficiency; AT: ataxia-telangiectasia; XLA: x-linked agammaglobulinemia; CGD: chronic granulomatous disease; WAS: Wiskott-Aldrich syndrome; HIES: hyper-IgE syndromes.

Immunological findings of IEI patients

White blood cell (WBC) in 47 (63.5%) and lymphocyte counts in 43 (79.6%) patients were within the normal range, while lymphopenia and lymphocytosis were reported in 5.6% and 14.8% of patients, respectively. **Table V** shows the spectrum of immunological findings in the study population.

The total count of lymphocyte subsets including CD3$^+$, CD8$^+$, CD19$^+$ and CD20$^+$ were within the normal range in 24 (41.4%), 30 (50.8%), 23 (44.2%), and 14 (56.0%) patients, respectively, while a decreased number of CD4$^+$ T cells was reported in 31 (52.5%) patients. The majority of patients with IEIs had a normal range of IgM and IgE (55.0% and 58.0%, respectively), while low IgG and IgA serum levels were reported in 47.5% and 50.7%, respectively.

In predominantly antibody deficiencies as the largest group (36.7% of patients), lymphocytosis was reported in most of the patients (11, 44.0%) and a high rate of CD8$^+$ T cells was

Table III *- Distribution of IEIs according to the 2019 Update of the International Union of Immunological Societies (IUIS) Phenotypical classification.*

Type	Number of cases (%)
Immunodeficiencies affecting cellular and humoral immunity	11 (12.2)
SCID	10
HIgM	1
Combined immunodeficiencies	25 (27.8)
CID	8
AT	7
WAS	5
HIES	4
ICF1	1
Predominantly antibody deficiencies	33 (36.7)
IgAD	13
CVID	9
XLA	7
IgG subclass deficiency	2
Hypogammaglobulinemia	2
Diseases of immune dysregulation	1 (1.1)
ALPS-like	1
Congenital defects of phagocyte number, function, or both	15 (16.7)
Neutropenia	6
CGD	5
Cyclic neutropenia	2
LADs	2
Defects in Intrinsic and Innate immunity	3 (3.3)
CMCC	3
Auto-inflammatory disorders	0 (0)
Complement deficiencies	2 (2.2)
Complement deficiency	1
Hereditary angioedema	1
Bone marrow failure	0 (0)
Phenocopies of IEI	0 (0)

reported in 9 (50.0%) patients; also the majority of patients were reported to have a low level of IgG, IgM and IgA (59.1%, 47.6%, and 64.3%, respectively). In the Combined immunodeficiencies with associated or syndromic features group (27.8% of patients), the frequency of $CD3^+$ and $CD4^+$ T cells were lower than the normal range in the majority of patients (50.0% and 55.0%, respectively). Moreover, low serum level of IgA was reported in 47.8% of the patients.

Discussion

IEI disorders are a heterogeneous group of genetic disorders associated with severe and recurrent infections, autoimmune diseases, and increased occurrences of malignancies (5). Although an increase in the number of specialists in the field of clinical immunology and increasing knowledge of practitioners have improved early diagnosis and management of this significant and rare group of disorders (15), IEIs are still underdiagnosed and there is a noteworthy diagnosis lag even in developed countries (9). Moreover, due to the lack of facilities, diagnosing IEIs continues to be a challenge in developing countries (6). It is worth mentioning that delayed diagnosis and misdiagnosis mainly reflect the poor knowledge about IEI among general practitioners/pediatricians. In this study, the median diagnostic delay was 1.5 (0.17-5.0) years, which was less than the previous cohort of 98 Iranian patients (6.1 years) in 2016 (4) and the Middle East and North Africa (MENA) Registry (3.4 years) (16). However, it was longer than the reported diagnostic delay (10 months) in the latest update on the Iranian National Registry of Primary Immunodeficiencies (10), as well as recent surveys in Pakistan (6) Oman (17), and Kuwait (18). In the present study, the diagnostic delay in HIES patients was longer than other PID patients. The first clinical manifestations are varied in HIES patients, so, the diagnostic delay may be high and they have been seen by a clinical immunologist too late. It is worth mentioning that in HIES patients, allergic reaction and elevated serum IgE level is one of the main manifestations that sometimes lead to misdiagnosis with an allergy and is treated as an allergic patient for years by non-immunologists. The longer the diagnostic delay, the greater and the worse long-term complications such as bronchiectasis, which per se lead to significant mortality and morbidity. Early recognition and prompt diagnosis of IEIs by raising the index of physicians' suspicion of these disorders helps in limiting significant disease-related mortality and morbidity and improves the patients' quality of life (19). Registration of Iranian IEI patients might have performed the main role in reducing the diagnostic delay since it raised the knowledge of medical staff about such disease. Of note, the available screening test for IEI is insufficient both at the national level and the nearby medical centers. As a consequence, some severe forms of IEI such as SCID might have died during infancy from severe infections before a definitive diagnosis is made (20).

In the present research study, the most common IEIs were IgAD, SCID and CVID. Therefore, the proportion of patients with IEI, who are are difficult to diagnose and prone to severe complications, has significantly raised. Previous cohort studies on IEI indicated that approximately all patients with IEI had

Table IV *- Clinical manifestations of inborn errors of immunity patients with full follow-up.*

Parameters	Total n (%)	Predominantly antibody deficiencies (%)	Combined immunodeficiencies with associated or syndromic features (%)	Congenital defects of phagocyte number, function, or both (%)	Immunodeficiencies affecting cellular and humoral immunity (%)	P-value
Pneumonia (n = 60)	31 (51.7)	58.3	44.4	16.7	71.4	0.192
Sinusitis (n = 54)	22 (40.7)	73.9	12.5	16.7	20	**0.001***
Otitis media (n = 55)	23 (41.8)	41.7	53.3	28.6	60	0.634
Bronchiectasis (n = 51)	5 (9.8)	23.8	0	0	0	0.079
Skin complications (n = 52)	24 (46.2)	22.2	72.2	40	16.7	**0.012***
Meningitis (n = 46)	4 (8.7)	6.3	12.5	0	0	0.720
Oral candidiasis (n = 52)	13 (25.0)	5.9	22.2	16.7	50	0.131
Septic arthritis (n = 42)	4 (9.5)	7.7	12.5	0	20	0.778
Malignancy (n = 54)	1 (1.9)	0	6.3	0	0	0.547
Hepatomegaly (n = 55)	14 (25.5)	36.4	0	42.9	14.3	**0.041***
Splenomegaly (n = 55)	11 (20)	30.4	6.3	16.7	0	0.157
Lymphadenopathy (n = 52)	18 (34.6)	42.1	23.5	83.3	0	**0.015***
Autoimmunity (n = 60)	19 (31.7)	40	28.6	0	20	0.253
Enteropathy (n = 42)	8 (19)	42.9	0	0	20	**0.022***
Clubbing (n = 51)	7 (13.7)	22.7	0	40	0	0.075
Failure to thrive (n = 54)	14 (25.9)	28	14.3	20	50	0.410
Conjunctivitis (n = 46)	6 (13.0)	33.3	0	0	0	**0.028***
Asthma/Allergy (n = 54)	15 (27.8)	20	33.3	25	33.3	0.793

*P-value is statistically significant < 0.05; n: number; skin complications include: psoriasis, vitiligo, rash, vasculitis and alopecia.

a history of recurrent infection before diagnosis was finalized (21, 22). In the current study also, 84.5% of patients represented different infections among which, pneumonia (51.7%) was the most common clinical manifestation in patients with IEIs that followed by skin complications (46.2%) and otitis media (41.8%). In this regard, a study in a single-center pediatric hospital in Northern Iran for 21 years represented pneumonia as the most frequent infectious manifestation in IEI patients (23). In another study in a single tertiary care center in China, the results of the clinical manifestations distribution were similar to the present study, in which respiratory infection including pneumonia was the most common complication (79.5%) and the second common complications were infections of the skin and mucous membranes (33.9%) (5). Other studies from Egypt (24) and Pakistan (6) presented almost the same results. Dermatological manifestations are common in IEIs and have been reported in up to 48% of patients with any of these pathologies (25). In the present study, skin complications was the second most common clinical manifestation (46.2%), almost similar to what is reported in the literature. Most of the patients with confirmed IEI present otitis as one of the recurrent infections (26). In the current study, the third most common clinical manifestation was otitis media (41.8%). Differences in the prevalence of clinical manifestations among different countries may be linked to the differences in data collection methods with the variable degrees of expertise and diagnostic facilities. However, poor availability and unaffordability of medicines might have made these severe complications much more prevalent among our patients. Patients with IEIs are frequently diagnosed based on a clinical history of recurrent infections due to less virulent or atypical pathogens (6), though, they can also present with non-infectious manifestations, such as autoimmune diseases

Table V *- Immunological findings of patients with inborn errors of immunity.*

Parameters	Total (n = 90)	Predominantly antibody deficiencies (n = 33)	Combined immunodeficiencies with associated or syndromic features (n = 25)	Congenital defects of phagocyte number, function, or both (n = 15)	Immunodeficiencies affecting cellular and humoral immunity (n = 11)	P-value
WBC × 10^3 (cell/μL), median (IQR) (n = 74)	7.550 (4.700-10.892)	8.800 (6.975-11.050)	8.400 (5.647-11.155)	4.070 (3.712-9.000)	5.400 (4.000-10.080)	**0.034***
Absolute lymphocytes counts × 10^3 (cells /μL), median (IQR) (n = 72)	2.603 (1.750-4.270)	3.312 (2.105-6.333)	2.112 (1.466-4.700)	2.477 (1.740-2.968)	2.052 (0.720-3.713)	0.148
Absolute neutrophils counts × 10^3 (cells /μL), median (IQR) (n = 68)	4.024 (1.848-6075)	4.071 (2.376-5.766)	4.335 (3.262-6.600)	1.768 (0.516-5.341)	2.268 (0.969-5.833)	0.147
$CD3^+$ T cells percentage, (n = 56)	70.0 (50.38-79.0)	74.0 (61.0-80.0)	64.7 (46.7-79.0)	79.7 (71.0-82.5)	12.0 (1.5-61.5)	**0.005***
$CD4^+$ T cells percentage (n = 57)	32.0 (17.4-4.25)	35.5 (24.0-40.1)	32.8 (20.0-41.0)	36.0 (29.7-49.0)	2.0 (0.8-13.5)	**0.004***
$CD8^+$ T cells percentage (n = 57)	30.0 (15.95-38.0)	32.0 (20.0-49.0)	30.0 (19.8-33.0)	30.0 (13.0-36.8)	11.1 (1.1-34.3)	0.139
$CD19^+$ percentage (n = 54)	15.5 (3.85-25.34)	6.0 (0.0-16.0)	18.0 (5.0-33.9)	10.0 (7.9-17.0)	50.0 (8.0-83.6)	**0.016***
$CD20^+$ percentage (n = 27)	18.0 (6.0-39.3)	16.7 (8.5-23.0)	21.4 (7.5-46.8)	9.5 (5.1-13.4)	43.0 (13.5-73.6)	0.180
IgG, (mg/dL), median (IQR) (n = 65)	464.0 (180.0-1135.5)	420.0 (97.5-1017.7)	672.0 (170.0-1203.0)	844.0 (471.5-2911.5)	211.0 (51.75-363.0)	**0.025***
IgA (mg/dL), median (IQR) (n = 70)	13.5 (3.2-73.77)	7.0 (0.0-18.0)	30.0 (1.0-156.0)	77.0 (15.25-257.0)	28.0 (6.25-64.0)	**0.018***
IgM (mg/dL), median (IQR) (n = 64)	57.0 (22.0-156.75)	40.0 (10.0-96.5)	90.0 (43.0-256.0)	156.0 (34.5-271.0)	35.5 (7.25-56.0)	**0.033***
IgE (mg/dL), median (IQR) (n = 52)	5.65 (1.0-165.0)	4.0 (0.0-10.0)	24.4 (1.02-796.75)	22.5 (10.2-587.5)	84.9 (0.0-165.75)	0.198

Ig: Immunoglobulin; WBC: white blood cell; the median is shown with 25^{th} and 75^{th} percentiles; *P-value is statistically significant < 0.05.

(27). Autoimmunity has often been recognized in connection with different forms of IEI (28). It is worth mentioning that, autoimmune disorders may be the first manifestation of the disease in some PID patients such as CVID (29). In the current study, autoimmunity was observed in 31.7% of patients while in patients with IgAD and CVID, the prevalence of autoimmunity was reported in 58.3% and 62.5% respectively. The frequency of autoimmunity in CVID patients (62.5%) was higher than other forms of predominantly antibody deficiencies as the largest IUIS group which is similar to previous studies (30).
Recently, the overall prevalence of autoimmunity in CVID patients was reported to be 29.8% in a systematic review study (31). Another study from Brazil reported autoimmune diseases in 61.5% of patients diagnosed (32) but in another study on Tunisian patients, the prevalence of autoimmunity was reported in 6.8% of IEI patients (33). One of the reasons for the difference between our data and other studies in the frequency of autoimmunity may be the difference in the study design. In the previous studies, the presence of immunodeficiency in patients with pure autoimmunity was investigated and identified several immunodeficient patients who were primarily diagnosed with pure autoimmune disorders (34).
Our data further showed that consanguinity and family history of IEI, seen in 59.2% and 36.4% respectively, were the most predictive factors for IEI diagnosis especially in a disease with an autosomal recessive pattern of inheritance (35). It is noteworthy that consanguinity has also been recognized as an important relevant factor for the high incidence of SCID, AT, and CGD, reported in Iran (36-38) and SCID in Kuwait (39).

The first report of IEI registry of Iran was published in 2002 consisted of 440 IEI patients (40). Recently, Iranian immunologists have published the 20-year survey of the IEI registry from the recently structured national IEI network organizing 31 collaborating hospitals affiliated to 26 medical science universities from the main provinces (10). In those surveys, 3056 patients were registered, while the majority were diagnosed with primary antibody deficiency (PAD) (29.5%). Based on the IUIS classification system, in our study, the most prevalent groups were predominantly antibody deficiencies (36.7%), combined immunodeficiencies with associated or syndromic features (27.8%), and congenital defects of phagocyte number, function or both (16.7%) groups. But in the fourth update on the Iranian National Registry of Primary Immunodeficiencies in 2018, among the newly diagnosed IEI patients, the autoinflammatory disorders group were the most common group (31.4%), followed by predominantly antibody deficiencies (22.2%) and combined immunodeficiencies with associated or syndromic features (18.6%) (10). In another study of 528 Indian children, the most common groups were Immunodeficiencies affecting cellular and humoral immunity and Congenital defects of phagocyte number, function, or both which accounted for 29% of all patients (41). In another study in Pakistan (42) and Egypt (43), Combined immunodeficiencies with associated or syndromic features (36.6%) and Immunodeficiencies affecting cellular and humoral immunity (30.0%) groups, were the most common groups respectively. It is important to know the prevalence of IEI groups among different countries to increase awareness, promote optimal treatment, support research in the field of disorders of immunity and facilitate recognition.

It would be quite challenging to estimate a total number of undiagnosed and unregistered IEI patients. This number, therefore, does not show the frequency and the burden of IEI in our study community. This is due to multiple limiting factors. First of all, it did not include patients with mild manifestations, who are usually managed as outpatients by general practitioners, pediatricians, or other specialists at various health centers and private clinics in the country. Also, asymptomatic IEI patients were not included in the study. Moreover, the present study contains some limitations, including limited molecular diagnostic data and small sample size. As the number of clinical immunologists and access to diagnostic tests at our center increased, we hope for a reduction in delayed diagnosis and early diagnosis of more patients in future years.

Conclusions

In conclusion, our study describes a sample of Iranian patients having a variety of IEIs with a high frequency of predominantly antibody deficiencies. Pneumonia and inflammatory skin complications showed widespread involvement as the clinical manifestations whereas pneumonia and fever were the most-frequent first presentation of IEIs. Physicians should suspect immunodeficiency disorder in patients with a history of recurrent infections and/or in complicated patients with inflammatory diseases that do not respond to treatment.

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Conflict of interests

The authors declare that they have no conflict of interests.

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