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RESEARCH ARTICLE

Retrospective Evaluation of Patients with Primary Immunodeficiency: Five Years of Experience

Primer İmmün Yetmezlik Tanısı ile Takip Edilen Hastaların Retrospektif Olarak Değerlendirilmesi: Beş Yıllık Deneyim

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ABSTRACT

Objective: This study aimed to gain a better understanding of the features of patients with primary immune deficiency diseases/inborn errors of immunity (PID/IEI) in our region.

Materials and Methods: In this study, the medical records of 1163 patients with IEI who had been followed up for 5 years were retrospectively reviewed.

Results: Of the patients, 714(61.3%) were boys and 449(38.6%) were girls. The mean age of diagnosis and diagnostic delay were found as 56.5 and 27.4 months, respectively. Immune deficiency linked to antibody deficiency comprised 90.2%(n= 1049)of all patients. The ratio and incidence of severe combined immunodeficiency(SCID) were 2.1% and approximately one in 10000 live-birth, respectively. The Complaints of respiratory tract infection and otitis media were significantly higher ($p<0.05$). The consanguinity percentage was 31.8%. First-degree cousin marriage was significantly higher in congenital defects of phagocyte, immune dysregulation, and combined immune deficiency than in other IEIs ($p<0.05$). The history of death of a previous sibling was 12.3%, IEI in the family was 10%, and growth and development retardation was 7.3% among our patients. While complete blood cell count(CBC) resulted in frequencies of anemia of 17.2%, neutropenia of 3.2%, lymphopenia of 5%, and thrombocytopenia of 1.9% in all patients, the lymphopenia ratio was 87% in those with SCID. Due to recurrent infections, 95.6% of patients were administered trimethoprim/sulfamethoxazole prophylaxis, and 5.8% received intravenous immunoglobulin replacement therapy. Forty-two percent of all patients were diagnosed with asthma during clinical follow-up, and chronic lung pathology was found in 7.8% of the patients.

Conclusion: This study reveals that primary immune deficiency frequency was found higher in Konya city than the stated prevalence in literature and consanguinity among parents may be a remarkable factor and the presence of lymphopenia may be a remarkable feature for SCID.

Keywords: Primary immunodeficiency, inborn errors of immunity, consanguinity, allergy, complication, childhood

ÖZET

Amaç: Bölgemizdeki Primer İmmün Yetmezlik / Doğuştan Bağışıklık Kusurları (PİY/ IEI) tanısıyla izlenen hastalarımızın özelliklerinin daha iyi anlaşılmasını sağlamaktır.

Gereç ve Yöntemler: Bu çalışmada beş yıllık bir sürede PİY tanısıyla takip edilen 1163 hastanın dosya kayıtları retrospektif olarak incelendi.

Bulgular: Hastalarımızın 714'ü (% 61,3) erkek ve 449'u (% 38,6) kızdı. Hastaların ortalama tanı yaşı 56,5 ay ve tanıda gecikme süresi ortalama 27,4 aydı. Hastalarımızın % 90,2'sini (n=1049) antikor eksikliğine bağlı immün yetmezlikler oluşturmaktaydı. Ağır kombine immün yetmezlik (AKİY) oranı %2,1 (n=23) ve görülme sıklığı yaklaşık olarak on bin canlı doğumda bir olarak tespit edildi. Hastaların başvuru yakınmaları arasında solunum yolu enfeksiyonları ve otitis media diğer başvuru yakınmalarına göre istatistiksel açıdan anlamlı olarak yüksekti ($p<0,05$). Hastalarımızın ebeveynleri arasında %31,8 oranında akraba evliliği yapıldığı saptandı. Birinci derece kuzen evliliklerinde fagositer sistem bozuklukları, immün sistemin regülasyon bozukluğuna bağlı hastalıklar ve kombine immün yetersizlikler diğer PİY'lere göre anlamlı olarak yüksek saptandı ($p <0,05$). Hastalarımızın % 12,3'ünde kardeş ölüm hikayesi, % 10'unun ailesinde ise PİY hikayesi ve % 7,3'ünde büyüme ve gelişme geriliği vardı. Tam kan sayımında anemi % 17,2, nötropeni % 3,2, lenfopeni % 5 ve trombositopeni % 1,9 oranında saptanırken AKİY tanılı hastalarımızda lenfopeni oranı % 87 idi. Tekrarlayan enfeksiyonlar nedeniyle %95,6 hastaya trimetoprim/sülfametoksazol profilaksisi ve % 5,8 oranında intravenöz immunglobulin destek tedavisi başlandı. Hastalarımızdan % 42'si klinik takibimizde astım tanısı aldı ve hastalarımızın % 7,8'inde ise kronik akciğer patolojilerinin varlığı saptandı.

Sonuç: Bu çalışma, Konya ve çevresinde PİY hastalıklarının literatürdeki sıklığından daha fazla görüldüğünü saptamış olup ebeveynler arası akraba evliliğinin önemli bir faktör oluduğunu ve lenfopeninin de AKİY hastalarında önemli bir özellik olabileceğini göstermiştir.

Anahtar Kelimeler: Primer immün yetmezlik, doğuştan bağışıklık kusurları, akraba evliliği, alerji, komplikasyon, çocukluk çağı

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INTRODUCTION

Inborn errors of immunity (IEI), formerly known as primary immunodeficiencies(PID), are a group of heterogeneous and hereditary disorders characterized by increased susceptibility to infections as a result of impairment in one or more of the immune system components, autoimmune diseases, and predisposition to the development of malignancy (1,2). When all innate immunity errors are considered, the incidence of these diseases is reported to be 1/2000–10,000 live births (1,3). Primary antibody deficiency is the most common type of IEI (4). The common clinical features of IEIs are the susceptibility to infections and the complaint of "having frequent infections." Classically, immunodeficiencies should be considered in children with a history of recurrent, severe infections that do not respond well to treatment or that result in complications (1-5). In this study, the clinical and laboratory characteristics of patients with inborn errors of immunity followed at our clinic were evaluated retrospectively to determine the regional features of patients with IEI by evaluating the clinical, laboratory, and sociodemographic variables.

MATERIALS AND METHODS

This study included 1163 patients with PID between 2006 and 2011. There were 5741 patients who were being followed up at the Department of Pediatric Allergy and Immunology during the same five year-period. This study was approved by our ethics committee (2012/32). PID diseases were classified according to the International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiencies(1). The International Union of Immunological Societies (IUIS) IEI Committee has divided PIDs into 10 classes according to their phenotypes, with the latest update(2).

The clinical, laboratory, radiological, and follow-up features of our patients with IEI were reviewed from the records of their Pediatric Immunology Cards and evaluated retrospectively. Consanguineous marriages were classified as those between first-degree (marriage between siblings' children), second-degree (marriage between siblings' grandchildren), and third-degree (more distant) relatives. If the height and weight measurements were below 2SD according to the normal values of Türkiye children, it was accepted as growth retardation. If absolute lymphocyte count (ALC) is less< 3000/mm^3 under one year of age and less than 1500/mm^3 over one year of age, lymphopenia was assessed, and if the absolute neutrophil count (ANC) was less than 1500/mm^3, it was assessed as neutropenia. Isohemagglutinin titers of less than 1/10 were significant.

Statistical evaluation of the data was performed using SPSS for Windows (version 20.0; SPSS Inc., U.S.A) software package. Fisher's chi-squared test and independent sample t-tests were used to compare the groups. Statistical significance was set at $P<0.05$.

RESULTS

Of the 5741 patients who visited the Department of Pediatric Allergy and Immunology during the five years between 2006 and 2011, 1163 were diagnosed with IEI. The annual number of patients who visited the outpatient clinics of the Department of Pediatrics was approximately 15.000 per year. According to this, approximately 1.5% of the patients who visited the outpatient clinics of the Department of Pediatrics and 20.2% of the follow-up patients at the Department of Pediatric Allergy and Immunology consisted of IEI cases.

Among 1163 patients with IEI, 714 (61.3%) were male and 449 (38.6%) were female, with a calculated male to female ratio of 1.59. The mean age at diagnosis of the patients was 56.5±58.3 months (1-996 months), the mean follow-up period was 12.1±15.3 months (0-117months) and the mean period of delay in diagnosis was 27.4 ±31 months (range, 1–438 months). Except for 9 cases, the rest of our patients were in the children's age group. The most commonly detected IEI in our patients was primary antibody deficiencies (PAD) (90.2%). This was followed by other non-well-defined immunodeficiency syndromes (4.9%), combined T and B-cell immunodeficiencies (2.5%), autoinflammatory diseases (1.02%), complement deficiencies (0.5%), phagocyte system disorders (0.25%), regulation disorders of the immune system (0.25%), and diseases characterized by a deficiency in the natural immune system (0.34%) (Table1). The rate of parental consanguinity was 31.8% (Table 2) in patients with IEI. The rate of consanguineous marriages was 74% in SCID, 66.7% in phagocytic system disorders, and 66.7% in diseases related to dysregulation of the immune system, 46.2% for common variable immune deficiencies, 43.3% for other well-defined immunodeficiencies, and 27% for antibody deficiencies. The rate of first-degree consanguineous marriage was found to be significantly higher in cases of phagocytic system disorder, diseases related to dysregulation disorders of the immune system, and combined immunodeficiencies than in other IEIs ($p<0.05$). Among these patients, 12.3% had a history of sibling death, 10% had a family history of IEI, and 7.3% had growth and developmental retardation.

The complaints of patients with IEI on admission were usually recurrent infections (Table 2). In patients with IEI, recurrent upper respiratory tract infections (URTI) were detected at a rate of 56.9%, asthma at a rate of 42%, recurrent lower respiratory tract infections (LRTI) at a rate of 17.2%, recurrent otitis media at a rate of 13.7%, sinusitis at a rate of 7.1%, gastroenteritis at a rate of 8.4%, oral moniliasis at a rate of 11.6%, urinary tract infection (UTI) at a rate of 3.4%, allergic skin findings at a rate of 3.2%, recurrent skin infections at a rate of 3.2%, recurrent lymphadenitis at a rate of 4.5%, sepsis at a rate of 1.9%, and meningitis at a rate of 0.2%. Upper and lower respiratory tract infections and otitis media were found at a significantly higher rate than other accompanying symptoms ($p<0.05$).

Anemia was detected in 200 patients (17.2%), neutropenia in 37 (3.2%), lymphopenia in 58 (5%), and thrombocytopenia in 22 (1.9%) with IEI. Neutropenia was detected in 66.7% of dysregulation disorders of the immune system, 33.3% in innate immune system defects, and 25% in combined immunodeficiencies and complement deficiencies

Table 1. The Classification Of Inborn Errors Of Immunity according to International Union of Immunological Societies (IUIS) 2019

	Female (N)	Male (N)	Total (N)	(IEI) %*(1163)
1. Combined T And B Cell Deficiencies	15	14	29	2.5
Severe Combined Immunodeficiency	10	13	23	2.1
Combined Immunodeficiency	1	-	1	0.08
CD3 Zeta Chain Deficiency	1	-	1	0.08
CD3 Gama Chain Deficiency	3	1	4	0.34
2. Antibody Deficiencies	388	661	1049	90.2
Transient Hypogammaglobulinemia Of Infancy	125	235	360	30.9
Unclassified Hypogammaglobulinemia	106	139	245	21
Physiological Hypogammaglobinemia	23	27	50	4.2
X-Linked Agammaglobulinemia	-	2	2	0.17
Autosomal Recessive Agammaglobulinemia	-	2	2	0.17
Common Variable Immunodeficiency	6	9	15	1.3
IgA Deficiency	76	99	175	15
Partially IgA Deficiency	65	78	143	12.2
Selective IgA Deficiency	11	21	32	2.72
IgM Deficiency	47	145	192	16.5
Partially IgM Deficiency	47	144	191	16.4
Selective IgM Deficiency	-	1	1	0.08
3.Other Well Defined Immunodeficiency Syndromes	31	28	59	4.9
Ataxia Telengiectasia	2	6	8	0.68
Nijmegan Breakage Syndrome	2	1	3	0.25
Bloom Syndrome	-	1	1	0.08
ICF Sendromu	-	1	1	0.08
Di George Syndrome	7	6	13	1.1
Hiper Ig E Syndrome	6	3	9	0.7
Down Syndrome	13	8	21	1.78
Kabuki Make-Up Syndrome	1	2	3	0.25
Cole Hughes Syndrome	-	1	1	0.08
4. Disease Of Immune Dysregulation	2	1	3	0.25
Chediak Higashi Syndrome	-	1	1	0.08
Griscelli Syndrome	2	-	2	0.17
5. Defects Of Phagocyte Number Or Function	1	2	3	0.25
Chronic Granulomatous Disease	1	2	3	0.25
6. Defects In Innate Immunity	4	-	4	0.34
IRAK4 Deficiency	1	-	1	0.08
Unknown Mutation	2	-	2	0.17
IL12R Deficiency	1	-	1	0.08
7. Autoinflammatory Disease	5	7	12	1.02
PFAPA Syndrome	4	7	11	0.94
8. Complement Deficiencies	3	3	6	0.5
9. Bone Marrow Failure	0	0	0	0
10. Phenocopies Of Inborn Errors Of Immunity	0	0	0	0

(p<0.05). Lymphopenia was found in 75% of combined immunodeficiencies, 66.7% with innate immune system defects, 33.3% with dysregulation disorders of the immune system, and 26.7% with other well-defined immunodeficiencies (p <0.05). Anergy was detected in 86 (7.4%) patients who underwent tuberculin skin tests. According to the tuberculin skin test, isoniazid prophylaxis was initiated in 24 (2.1%) patients, and this condition was found at a significantly higher rate in phagocytic system disorders and complement system deficiencies (p<0.05). The isohemagglutinin titer was below 1/10 in 121 (10.4%) patients at admission. In the examination of peripheral blood lymphocyte subgroups, at least one subgroup was abnormal in 132 patients (36%). High specific IgE levels and/or positive skin prick test results were detected in 108 (9.3 %) patients.

The tonsils of 31 patients (2.7%) were found to be hypoplastic on physical examination. Hypoplastic tonsils were present in 51.9% of patients with combined immunodeficiency and in 50% of patients with innate immunity defects. Lymphoid tissue hypoplasia other than the tonsils was present in 50% of the patients with combined immunodeficiency and 33.3% of the patients with dysregulated diseases (p<0.05). Organomegaly was detected in all patients with immune dysregulation diseases, in 75% of the patients with phagocytic

Table 2. Demographic Data, Diagnostic Delay And Clinical Features Indifferent studies

	Number of IEI paients	M/F rate	Age of diagnosis (months)	Age of onset of symptoms (months)	Diagnostic delay (months)	Follow-up time	Consanguinity rate	Clinical features
Razael N et al.	930	1.7	24	-	31	-	68.5%	20% pneumonia 13% diarrhea 10% sinusitis 9% otitis media
Shabestari MS et al.	59	1.56	57	-	12	-	54%	67% pneumonia 29% diarrhea 28% sinusitis
Kılıç SS et al.	1435	1.56	4.71 (0-62)	2.47 (0-49)	26.9 (10-540)	-	14.3%	pneumonia sinusitis otitis media
Aldırmaz S et al.	168	1.76	52.8 (5-216)	-	-	-	16%	90.5% URTI 38.8% pneumonia 22.4% sinusitis
Kılıç M et al.	78	1.6	5.4 (0.4-19)	3 (0.1-180)	28.9 (0.2-108)	-	30.8%	65.4% pneumonia 55% URTI 16.7% diarrhea
Mohammadine jad P et al.	307	1.51	96 (1 month-56 years)	-	1.25 years (1week-28 years)	-	59%	36.5% pneumonia 21.8% diarrhea 15.6% sinusitis
Al-Tamemi S et al.	90	1.57	24 (1 week-16 years)	9 (1-144)	-	-	81%	42% pneumonia 27% abscess 12% BCGitis

system disorders, in 46.4% of the patients with combined immunodeficiency, and 33.3% of the patients of the patients with innate immunity defects ($p<0.05$).

We found that 95.6% of our patients were followed with antibiotic prophylaxis (trimethoprim/sulfamethoxazole: TMP-SMX), and 5.8% of the patients were treated with intravenous immunoglobulin (IVIG) replacement therapy. Radiological evaluation revealed chronic lung pathologies in 91 (7.8%) patients (16 patients with bronchiectasis, 1 patient with fibrotic changes, 2 patients with fungus, 1 patient with pleural thickening, 1 patient with bronchiolitis obliterans, and 1 patient with ground glass opacity and nodule), and asthma in 474 (42.1%) patients.

Between 2006 and 2011, there were an average of 35-38 thousand live births annually in Konya, and the population of Konya was approximately one million inhabitants. On average, about four to five patients are diagnosed with SCID annually among the patients who were admitted to our hospital from Konya. According to this, the SCID prevalence in our region can be estimated as approximately 1 out of 10.000 live births and the IEI prevalence as 1 in 1000 births. Consanguineous marriage was present in 17 (74%) of 23 patients diagnosed with SCID. Of these, 13 (52%) were first-degree relative. T-B-NK+ SCID was found in 13 patients, T-B+NK+ SCID in 2, T-B-NK- SCID in 2, and T-B+NK- SCID in six patients were classified according to peripheral blood lymphocyte subgroups. The ARTEMIS (n=2), ADA (n=2), JAK3 (n=2), RAG2 (n=1), and Gamma chain (X-linked SCID) (n=1) gene mutations were detected in 8 SCID patients whose mutation analysis could be studied, while one patient was also diagnosed with the Type III BLS (Bare Lymphocyte Syndrome) gene defect. According to the clinical findings detected in our SCID patients at the time of admission, LRTI were found at a rate of 69% (16), moniliasis at a rate of 73% (17), gastroenteritis at a rate of 56% (13), and sepsis at a rate of 39% (9). Nine (39%) patients had growth and developmental retardation and 20 (87%) patients had lymphopenia. Bacillus Calmette-Guérin (BCG) infection was observed at a rate of 13%, absence of thymus at a rate of 87% (20). All patients with SCID were treated with IVIG, TMP-SMX, and antifungal prophylaxis. The mean age at diagnosis of the 23 patients diagnosed with SCID (10F/13M) was 9.3±10.3 months (1-24 months), the mean age at the time of the study was 34±20.6 months (5-227 months), and the mean time of delay in diagnosis was 3.5±5.7 months (0-21 months). Twelve (52.1%) patients with SCID underwent hematopoietic stem cell transplantation (HSCT). Eight of these patients had T-B-SCID, four had T-B+SCID, and none of these patients were lost. The other 10 patients diagnosed with SCID died and one patient

Table 3. Distribution Of Inborn Errors Of Immunity In Different Studies

	1 Combined T and B cell deficiencies (%)	2 Antibody deficiencies (%)	3 Other well defined immunodeficiency syndromes (%)	4 Disease of immune dysregulation (%)	5 Defects of phagocyte number or function (%)	6 Defects in innate immunity (%)	7 Autoinflammatory disease (%)	8 Complement deficiencies (%)
Al-Tamemi S et al.	12	18	13	3	42	-	-	6
Carneiro-Sampaio M et al.	6.7	60.8	8.3	5.2	8.7	5.9	1.2	2.8
Mohammadinejad P et al.	11.7	38.4	16.9	3.6	14.7	1	11.4	2.3
Gathmann B et al.	7.78	55.2	15.6	3.74	8.4	0.78	1.95	4.6
Ödek Ç et al.	17.3	56.2	11.3	4.2	6.7	1	0.5	1.1
Aghamohammadi A et al.	22.3	32.3	17.2	2.6	17.4	1.6	5.2	1.4
Kilic SS et al.	2	73.9	5.5	0.7	3.5	1	13.3	0.4
Kılıç M et al.	7.7	71.8	10.3	-	1.3	-	-	5.1
DUR O et al.	12.4	81.4	2.2	0.5	1.5	0.25	0.5	1
ESID	7.6	56.14	15.16	3.7	8.6	0.97	1.94	4.1
Levia LE et al.	9.5	53.3	22.6	3.3	8.6	-	-	2.8
Razael N et al.	11	38.3	17.7	2.4	28.3	-	-	2.4
Sanal et al.	14	42	15	7	10	2	3	2
Yorulmaz A et al.	2.4	92.8	1.7	0.9	0.4	-	-	0.1
Our Study	2.5	90.2	4.9	0.25	0.25	0.34	1.02	0.5

with ADA deficiency was treated with ADA enzyme therapy.

DISCUSSION

The incidence of IEI in developed countries ranges from 1/10.000 to 1/100.000 (1). Although the exact incidence of IEI is not known in our country, where consanguineous marriages are common, it is expected that those with autosomal recessive inheritance are seen more commonly (3).

Mısırlıoğlu et al. reported that 2.1% of patients who visited their outpatient clinic had an IEI (4). In a previous study from our clinic, Yorulmaz et al. reported that about 25% of patients who applied to the outpatient clinic of Pediatric Allergy and Immunology and about 1% of patients who applied to the outpatient clinics of pediatrics had an IEI (3). In our study, approximately 1.5% of the patients visited the outpatient clinics of Pediatrics, and 20.2% of the patients followed the Department of Pediatric Allergy and Immunology consisted of IEI cases. The prevalence of IEI has been reported to be 3.72/100.000 in France (5), 4.4/100.000 in Oman (6), and 4.7/100.000 (7) in Qatar. The prevalence of IEI has been reported to be 30.5/100.000 in Türkiye (8). Although our study is not a prevalence study, Konya has a higher IEI and SCID prevalence than in the literature, and it supports the claim that IEI diseases are more common in our country.

PAD is the most common type of IEIs in children (8-15). This rate was reported as 18-61% in different countries and 56%-84.5% in Türkiye (6,8,12,16-22). The ratio of PAD (90.2%) in our study was higher than that reported in the literature and similar to the a previous study by Konya (3) (Table 3). This finding is because all types of IEIs are being followed at our department, which is the unique pediatric immunology center until 2011 in Konya, and our registry system is very good and sufficient to evaluate IEIs.

Previous studies have reported that IEI is more common in males. This finding depends on the M/F ratio of 1.5-1.7 in Iran (12,15,17), 0.56 in Brazil (21) and 0.58 in Germany (20). The M/F ratio has been reported as 1.36-3.2 in studies from Türkiye (4,3,8,19,22,23). Our study was also similar to these studies as having a male/female ratio of 1.59 and supports the claim that IEIs are seen at a higher rate among males.

The age of diagnosis and the diagnostic delay of IEI patients may vary in different studies as 1-8 years and 12-31 months (8,12,17,22), respectively. In the study by Yorulmaz et al., the age of diagnosis was 55.5 months and the delay in diagnosis was 24.3 months. In our study, the mean age at diagnosis was 56.5 months and and the delay in diagnosis was 27.4 months. Nine patients were adults. Because we are the only immunology center in the province where we are located, and because of our adult patients, our age at diagnosis and delay in diagnosis were found to be high compared to some studies (Table 2).

In our country, parental consanguinity varies according to region, but it has been reported to be approximately 32% (24). The parental consanguinity rates in patients with IEI have been reported as 14.3-68.5% in previous studies (3,4,6,20,21,25). In our study, parental consanguinity was found to be 31.8% among all IEI patients, and when compared with the study by Yorulmaz et al. (38%) in Konya between 2001 and 2006, the fall in the rate of parental consanguinity of IEI patients was remarkable. This finding suggests that the rate of parental consanguinity in our patients with IEI may change over time and has a downward trend due to migration to our region, but it is still high. Consanguineous marriage increases the risk of autosomal recessive diseases (3,10). In our study, only

one patient has X-linked inheritance, and consanguinity was found in 75% of patients with SCID. It is also important to identify genetic defects in patients with SCID because genetic counseling and prenatal diagnosis are required. Prenatal diagnosis can be made using amniocentesis and chorionic villus sampling for new pregnancies in cases with known genetic defects.

There could be a history of sibling death and a family history in patients with IEI. This prevalence was reported as 22-43.5% in Türkiye (3,16). In our study, 12.3% of the patients had a history of sibling death, and 10% had a family history of IEI. This low rate could be explained by the fact that the majority of our patients with IEI had PAD, which has a good survival rate with less severe disease without complications and death.

An increased incidence of infections in patients with IEI has been reported previously. In these studies, recurrent upper and lower respiratory tract infections, chronic diarrhea, and persistent oral candidiasis were common in patients with IEI (3,6,8,17,22,26). In our study, recurrent upper respiratory tract infections were found as the most common first admission complaint (56.9%), and asthma as the second most common (42%) and recurrent lower respiratory tract infections as the third most common (17.2%). These findings indicate that patients with IEI most commonly present with upper and lower respiratory tract infections and/or problems. Cytopenias are other warning signs of immunodeficiency for clinicians. The diagnosis of SCID is a pediatric emergency and early diagnosis is a life-saving approach. Although lymphopenia is present in almost all patients with SCID, it should be noted that these patients can have normal lymphocyte counts (3). Among our patients with SCID, 87% had lymphopenia and 13% had normal lymphocyte counts at admission. If the patient's medical history and physical examination are compatible with immunodeficiency, IEI should be considered, and advanced immunological evaluation should be performed even if the first-line immunological laboratory examinations are normal.

The incidence of SCID/CID in patients with IEI was reported as 2.5-22.5% in registry systems and literature (6,8,12-15,17-22). Yorulmaz et al. (3) reported that SCID was 2.4% among IEI patients between 2001 and 2006 in Konya (3) and we also found as 2.5% between 2006 and 2011 in the present study. The prevalence of SCID was estimated as approximately one in 10.000 live births in Konya and higher than one in 50-100 thousand in the literature (3). This was estimated to be the same as in the present study. This rate showed that SCID incidence was very high in Konya and did not change during a ten- year period. However, as there could be patients with SCID who applied to other health institutions without referring to our center and died before they could be diagnosed, we believe that the incidence of SCID in Konya is even higher than we estimated.

The most important problem with SCID is that early diagnosis is not possible because of a long delay in diagnosis. Al-Herz et al. reported a delay in the diagnosis of SCID of 7.5 months (27), and Reda et al. reported it as 6.6 months (28). In Europe, this is approximately 2.5-7 months (29). In Türkiye, the delay in the diagnosis of SCID is approximately 2–9 months (3, 16, 22, 30-34). (Table 2). In a previous study conducted between 2001 and 2006 at our center, Yorulmaz et al. reported that the mean delay in diagnosis was approximately 9 months (3). In our study, the delay in diagnosis was approximately 3.5 months between 2006 and 2011. It is noteworthy that the delay in diagnosis decreased from 9 to 3 months. This decrease is due to the training meetings held by our center to increase IEI awareness among physicians in Konya (34). This has also reduced the mortality rate after HSCT without organ complications, and was due to early diagnosis, resulting in a high survival rate in our patients.

In conclusion, patients with IEI are common because of the high rate of consanguineous marriages in our country. It is crucial to increase awareness of symptoms suggesting immunodeficiency among physicians who first evaluate these patients. In patients with recurrent and severe infections, it is essential to consider IEI diseases in the differential diagnosis and to prioritize immunologic evaluation so that these patients can be diagnosed at an early stage and treated early. As early diagnosis will save lives, the quality of life of patients and their families will increase, and it will be possible to provide genetic counseling or prenatal genetic diagnoses to families. For this purpose, it is important to establish awareness about warning symptoms for immunodeficient patients during medical education and training after graduation..

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