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Evaluation of Patients with Combined Immunodeficiency: A Single Center Experience

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ABSTRACT

Background: Severe combined immunodeficiency (SCID) is the most severe form of inborn errors of immunity (IEIs) and typically leads to death within the first year of life. Combined immunodeficiencies (CID) are immune disorders that are less severe than SCID and are characterized by qualitative or quantitative defects in T and B cells.

Objectives: To explore the clinical, laboratory, and genetic diagnostic approaches for patients diagnosed with SCID and CID.

Methods: In this retrospective single-center study, we evaluated 54 patients diagnosed with SCID and CID between 2006 and 2019.

Results: The male to female ratio was 30:24 and the rate of consanguinity was 77.8%. Among the patients, 23 were diagnosed with SCID and 31 diagnosed with CID. The most common phenotype in the SCID group was T-B-NK+ while in the CID group it was MHC class II deficiency. The median age at symptom onset for SCID and CID were 1 month and 5 months, respectively, while the median age at diagnosis was 4 months for SCID and 11 months for CID. The age at diagnosis of SCID and the age at diagnosis of symptoms were earlier than CID ($P<0.05$). Lymphopenia was present in 90.9% of patients with SCID and 51.6% of patients with CID ($P<0.05$). HSCT was performed in 10 out of 23 (43.4%) SCID patients and 10 out of 31 (32.2%) CID patients (total of 20 out of 54, 37%). The survival rates of SCID and CID patients who underwent HSCT were 80% and 70%, respectively.

Conclusions: Consanguineous marriage, sibling death and family members with similar characteristics should be investigated for early diagnosis. Further investigations should be performed in the presence of lymphopenia. With the increasing number of genetic diagnosis facilities and HSCT centers, the survival rate of patients is expected to rise.

Keywords: Severe combined immunodeficiency, Combined immunodeficiency, Growth retardation, Lymphopenia, Hematopoietic stem cell transplantation.

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INTRODUCTION

Severe combined immunodeficiency (SCID) is a diverse group of inherited diseases that result in a T-cell deficiency which may also be accompanied by a deficiency of B-cells or NK-cells. This condition leads to early-onset severe infections and growth retardation (1, 2). SCID is the most severe type of inborn errors of immunity (IEIs) and typically results in a fatal outcome within the first year of life if treatment such as hematopoietic stem cell transplantation (HSCT), or correction of certain defects by gene therapy or enzyme replacement therapy is not administered (1-3).

Combined immunodeficiencies (CID) are immune disorders characterized by qualitative or quantitative defects in T and B cells. The majority of these disorders are caused by hypomorphic mutations in the genes encoding molecules involved in T-cell post receptor transduction pathways or T-cell function. In addition to increased susceptibility to infections, CID presents a wide clinical diversity, characterized by conditions such as autoimmunity, inflammatory diseases, lymphoproliferation, and an increased risk of malignancy (1, 2). Based on data from neonatal screening programs, the overall incidence of SCIDs in Western countries is approximately 1 in 50,000 live births (4). The incidence of autosomal recessive diseases, including SCID and CID, is evidently greater in our country than in Western countries due to the higher prevalence of consanguineous marriages (1, 5, 6).

In a study conducted in our country, 1,054 patients diagnosed with IEIs were evaluated retrospectively between 2001 and 2006. The incidence of SCID was found to be 1 in 10,000 (5). The aim of our study was to examine the clinical, laboratory, treatment and follow-up outcomes of patients with SCID and CID.

MATERIALS AND METHODS

A cohort of fifty-four patients diagnosed with 23 cases of SCID and 31 cases of CID between 2006 and 2019 were enrolled in this study. Ethics approval for the study was granted by the Clinical Research Ethics Committee of the University of Health Sciences, Ankara Child Health and Diseases, Hematology Oncology Health Application and Research Center (Approval ID: 2018-162). The diagnostic criteria outlined by the European Society for Immunodeficiencies (ESID) served as the basis for diagnosing SCID and CID (7).

Retrospectively, demographic data, symptoms at hospital admission, age of symptom onset, age at diagnosis, the time interval between symptom onset and diagnosis, clinical and laboratory findings, treatment modalities, clinical follow-up, and survival data were extracted from patient medical records.

Hematological assessments, including a complete blood analysis, were conducted using an automated blood analysis device (ADVIA 2120i, Siemens Diagnostics, Marburg, Germany). Nephelometric methods (BN II system, Siemens Diagnostics, Munich, Germany) were used to measure the levels of IgG, IgA, IgM, and IgE. Lymphopenia was defined as an absolute lymphocyte count less than 3,000/mm3 for patients under one year old and 1,500/mm3 for patients older than one year. The peripheral blood lymphocyte subgroups, HLA-ABC, HLA-DR and DOCK8 expression, as well as in vitro lymphoproliferative response to phytohemagglutinin (PHA) were analyzed using flow cytometry (Cytomics FC500; Beckman Coulter, Miami, FL, USA). Normal limits for serum immunoglobulins were referenced from the study by Aksu *et al.* (8), and normal values for peripheral blood lymphocyte subgroups according to age were obtained from the study by Ikinciogullari *et al.* (9).

The 22q11.2 deletion was detected through fluorescence in situ hybridization (FISH). Molecular genetic analyses, including whole exome sequencing (WES) or targeted gene panels employing next-generation sequencing (NGS) techniques, were also conducted at

various centers. Clinical interpretation of the variants was performed according to the 2015 American College of Medical Genetics and Genomics (ACMG) guidelines utilizing the VarSome variant classifier tool (10).

Statistical Analysis

The data analysis was performed using SPSS version 23.0, a statistical software package (IBM SPSS Statistics for Windows, Ver 23.0; Armonk, NY; IBM Group Corp.). The normality of the distribution of continuous variables within groups was assessed using the Shapiro-Wilk test. Subsequently, the Mann-Whitney U test was used for pairwise comparisons of nonnormally distributed data, while the Kruskal Wallis test was utilized for comparisons involving more than two groups. Categorical data were analyzed using the chi-square test. A P value<0.05 was considered to indicate statistical significance.

RESULTS

Fifty-four patients were included in the study: 23 (42.6%) were diagnosed with SCID, and 31 (57.4%) were diagnosed with CID. Within the SCID group, the predominant phenotype was T-B-NK+SCID, which accounted for 61% (n=14) of the patients, while MHC class II deficiency was the most prevalent phenotype in the CID group, affecting 29% (n=9) of the patients. The diagnostic distributions of patients with SCID and CID are displayed in Table 1.

The distribution of sex revealed that 56.5% of the SCID patients were male, while 43.5% were female. Similarly, in the CID group, 54.8% were male and 45.2% were female. These two groups did not significantly differ in terms of sex distribution (Table 2). Furthermore, there were no statistically significant differences in parental consanguinity (77.8% for SCID and 77.4% for CID) or positive clinical history in the extended family (43.5% for SCID and 45.2% for CID) (Table 2).

The median age of onset, age of diagnosis, and diagnostic delay were 1 (0.5-8), 5 (1-11), and 2 (0-7) months, respectively, in the SCID patients. One patient (1.85%) whose sibling had SCID was diagnosed before the patient's symptoms started. In CID patients, the median age of onset, age of diagnosis, and diagnostic delay were 4 (1-96), 11 (2-216), and 9 (1-198) months, respectively. The age of onset and diagnosis were significantly

Table 1. Diagnostic distribution of SCID and CID patients

	Diagnosis	n (%)
SCID	T-B-NK+	14 (61)
	T-B+NK+	7 (30)
	T-B+NK-	2 (9)
CID	MHC class II deficiency	9 (30)
	DOCK8 deficiency	6 (20)
	Omenn syndrome	4 (13)
	PNP deficiency	3 (10)
	ARPC1B deficiency	2 (6)
	Coronin1A deficiency	2 (6)
	TTC7A deficiency	1 (3)
	Complete DiGeorge syndrome	1 (3)
	RAG1 deficiency	1 (3)
	DCLRE1C (Artemis) deficiency	1 (3)
	MHC class I deficiency	1 (3)

Table 2. Demographic characteristics of the SCID and CID patients

		SCID (n=23; 42.6%)	CID (n=31; 57.4%)	P
Gender [n (%)]	Male	13 (56.5)	17 (54.8)	1,000
	Female	10 (43.5)	14 (45.2)	
Consanguinity [n (%)]	Yes	18 (78.3)	24 (77.4)	1,000
	No	5 (21.7)	7 (22.6)	
Family History [n (%)]	Yes	10 (43.5)	14 (45.2)	1,000
	No	13 (56.5)	17 (54.8)	
Age of onset of symptoms (month)	Median (range)	1 (0.5-8)	4 (1-96)	0.003*
Age of diagnosis (month)	Median (range)	5 (1-11)	11 (2-216)	0.001*
Delay indiagnosis (month)	Median (range)	2 (0-7)	9 (1-198)	0.006*

*P value is statistically significant<0.05

earlier in SCID patients compared to CID patients (P<0.003 and P<0.001, respectively). The diagnostic delay was shorter in the SCID patients than in the CID patients (P<0.006) (Table 2).

Clinical Features of the Patient

The most documented clinical manifestations in SCID patients were lower respiratory tract infections (LRTIs) (n=17, 73.9%), oral moniliasis (n=15, 65.2%), gastrointestinal tract infections (n=8, 34.8%), growth retardation (n=8, 34.8%), and sepsis (n=7, 30.4%) (Table 3). Similarly, for the CID cohort, LRTI (n=27, 87%), growth retardation (n=21, 67.7%), fungal infections (n=12, 38.7%), gastrointestinal tract infections (n=10, 32.3%), sepsis (n=10, 32.3%) and upper respiratory tract infections (n=11, 35.5%) were frequently documented (Table 4).

Table 3. Infections and other findings in patients with SCID

Type of infection	n (%)
LRTI*	17 (73.9)
Oral moniliasis	15 (65.2)
Gastrointestinal tract infections	8 (34.8)
Sepsis	7 (30.4)
URTI**	6 (26.1)
CMV	3 (13)
Skin abscess	1 (4.3)
Suppurative otitis	1 (4.3)
Meningitis	1 (4.3)
Myocarditis	1 (4.3)
Other findings	
Growth retardation	8 (34.8)
Ulcerated wound in the mouth	2 (8.7)
Skin and mucosal findings	2 (8.7)
Chronic changes in the lungs (bronchiectasis and fibrotic changes in the lung)	2 (8.7)
Congenital heart disease	1 (4.3)

*LRTI: lower respiratory tract infection; **URTI: upper respiratory tract infection

Table 4. Infections and other findings in patients with CID

Type of Infection	n (%)
LRTI	27 (87)
Fungal infection*	12 (38.7)
Gastrointestinal tract infections	10 (32.3)
Sepsis	10 (32.3)
URTI	11 (35.5)
CMV	6 (19.4)
Skin and soft tissue infection	6 (19.4)
Wart	6 (19.4)
Suppurative otitis media	5 (16.1)
Organ abscess**	5 (16.1)
Varicella infection	3 (9.7)
Pulmonary tuberculosis	3 (9.7)
Meningitis	1 (3.2)
Myocarditis	1 (3.2)
Other findings	
Growth retardation	21 (67.7)
Skin and mucosal findings***	18 (58)
Chronicchanges in the lung****	11 (35.5)
Hepatosplenomegaly	5 (16.1)
Lymphadenopathy	5 (16.1)
Cholangitis	5 (16.1)
Malignancy*****	4 (13%)
Hematologic findings******	3 (9.7)
Congenital heart disease	2 (6.5)

*Oral moniliasis, chronic mucocutaneous candidiasis, **Lung abscess, hepatic abscess, empyema, ***Atopic dermatitis, erythroderma, ulcerated sore in the mouth, ****Bronchiectasis, fibrotic changes in the lung, *****Small bowel sarcoma, non-hodgkin lymphoma in the brain, intestinal plasmacytoma, nodular sclerosing type hodgkin lymphoma, ******Pancytopenia, immune thrombocytopenic purpura, autoimmune hemolytic anemia

Table 5. Evaluation of laboratory data from SCID and CID patients

		SCID	CID	P
Leukocyte count (mm^3)	Median (Min-Max)	3,400 910–13,650	1,050 1,400 – 103,900	0.011*
ALC (mm^3)	Median (Min-Max)	640 100 – 4,910	1,600 160 – 66,946	0.001*
ANC (mm^3)	Median (Min-Max)	2,100 280 – 12,610	2,610 190 – 2,2200	0.214
AEC (mm^3)	Median (Min-Max)	50 0 - 430	170 0- 3,9300	0.001*
IgG (mg/dl)	Median (Min-Max)	171 33-1,260	556 13-2,060	0.026*
IgA (mg/dl)	Median (Min-Max)	6 5-240	40 5-780	0.09
IgM (mg/dl)	Median (Min-Max)	15 4-214	47 4-133	0.004*
IgE (IU/ml)	Median (Min-Max)	9 0-111	18 5-3,8000	0.012*
CD3+CD16-CD56- (mm^3)	Median (Min-Max)	12 0-481	960 36-60,251	0.001*
CD3+CD4+ (mm^3)	Median (Min-Max)	7.3 0-196	478 24-22,761	0.001*
CD3+CD8+ (mm^3)	Median (Min-Max)	3 0-647	514 12-37,489	0.001*
CD3-CD16+CD56+ (mm^3)	Median (Min-Max)	196 3,8-2,399	324 22-5,355	0.199
CD19+ (mm^3)	Median (Min-Max)	9 0-4,419	261 9,6-4,680	0.007*
CD4+CD45+RA+ (mm^3)	Median (Min-Max)	1 0-12	9 0,2-82	<0,001*
CD4+CD45+RO+ (mm^3)	Median (Min-Max)	2,5 0-36	14 2-92	<0,001*

AEC: Absolute eosinophil count, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, *P<0,05

Immunological Findings

Lymphopenia was detected in 90.9% of patients diagnosed with SCID and and in 51.6% of patients diagnosed with CID. The frequency of lymphopenia was higher in patients with SCID compared to patients with CID (P<0.05). Eosinophil counts were more frequently reported in patients in the CID group than in those in the SCID group (P<0.05) (Table 5).

IgG levels were found to be low in 69.6% of patients with SCID and 58.1% in of patients with CID. The median IgG, IgM, and IgE levels of patients with SCID were significantly lower than those of patients with CID (P<0.05) (Table 5).

CD3+CD16-56-, CD3+CD4+ and CD3+ CD8+ T-cell levels were found to be low in all patients with SCID. Additionally, the CD3+CD16-CD56-, CD3+CD4+, and CD3+CD8+ T cell counts in patients with SCID were lower compared to those in patients with CID (P<0.05). The median counts of CD3+CD16-CD56-, CD3+CD4+, CD3+CD8+,CD4+CD45+RA+, and CD4+CD45+RO+ T-cell, as well as CD19+ B-cells were significantly lower in patients with SCID than in patients with CID (P<0.05). The laboratory parameters for patients with SCID and CID can be found in Table 5.

To assess the lymphocyte proliferation response, lymphocytes from 35 patients were stimulated with phytohemagglutinin (PHA). Notably, lymphocytes from 8 out

Table 6. In vitro evaluation of the lymphoproliferative responses in 35 patients with SCID and CID using phytohemagglutinin (PHA)

Lymphoproliferativeresponse	Very low n (%)	Decreased n (%)	Normal n (%)
SCID (n: 11)	8 (72.7)	3 (27.3)	0 (0)
CID (n: 24)	3 (12.5)	7 (29.2)	14 (58.3)
Total	11 (31.4)	10 (28.6)	14 (40)

of 11 SCID patients exhibited a very low response (<20%), while 3 had a decreased response (20-40%). Similarly, in the CID group, lymphocytes from 3 out of 24 patients had a very low response, 7 had a decreased response (20-40%), and 14 had a normal response (>40%) (Table 6).

Genetic Analysis

The 22q11.2 deletion was identified in one patient who was diagnosed with complete DiGeorge syndrome. This diagnosis was based on severe T-cell deficiency and specific clinical features. Variants that aligned with the clinical and laboratory data were found in 18 patients who underwent molecular genetic analysis. Fourteen of these variants had not been previously reported. The characteristics of the identified mutations and their effects on these patients are presented in Table 7.

Treatment and Prognosis

Ten out of the 23 patients with SCID underwent HSCT, and 8 of them survived. Of those who had the procedure, two died, while 13 patients who did not undergo HSCT died. The survival rate for SCID patients who underwent HSCT was 80%. Similarly, ten out of 31 patients with CID underwent HSCT, with 7 surviving, resulting in a survival rate of 70%. All SCID patients who could not undergo HSCT died. Additionally, of the 21 CID patients who were unable to undergo HSCT, only 6 were alive (28.5%) (Table 8).

DISCUSSION

SCID is the most severe form of IEI due to T-cell deficiency and may also be accompanied by B-cell or NK-cell deficiency, which manifests as early-onset severe infections, prompting HSCT in the first year of life. Lymphopenia is the most important laboratory indicator in the diagnosis of T-cell deficiencies (11). The only curative treatment for SCID is HSCT (or for certain forms of gene therapy); untransplanted individuals succumb to infections during the initial years of life (1).

There are regional differences in the prevalence and genetics of SCID. In Turkey, the most commonly reported SCID phenotype is T-B-. This phenotype accounts for 55% of all SCID cases in Turkey (12-14). Likewise, we also found the T-B-SCID phenotype to be the most common.

T- B- SCID is autosomal recessive in nature and is common in eastern societies where consanguineous marriages are more prevalent. Studies from countries with low rates of consanguineous marriage have found X-linked SCID (*IL2RG*) to be the most common type, with the T-B- phenotype reported in only 29.5% of SCID patients who underwent HSCT (15). The results from Turkey are more similar to those from Iran, where the T-B- SCID phenotype was reported to be 66-75% (16, 17).

The male/female ratio of the patients included in our study was 1.25. Studies conducted in Italy and North America also reported similar rates to our study (18, 19). Luke *et al*. and Yao *et al.* reported that male patients were in the majority in their studies, with male/female ratios of 4.2 and 10, respectively (20, 21). According to these two studies, the higher male sex ratio may be due to the majority of patients having an X-linked SCID.

Table 7. Characteristics of the identified mutations and their impacts on patients (n=18)

Patient	Gene	Variant	Protein	Zygosity	Variant type	Nonreported/ reported	ACMG	Clinical presentation
1	TRAC	c.181del	p.Ala61LeufsTer49	Homozygous	frameshift	Nonreported	VUS	SCID (T-B-NK+)
2	TRAC	c.181del	p.Ala61LeufsTer49	Homozygous	frameshift	Nonreported	VUS	SCID (T-B-NK+)
3	JAK3	c.3076A>T	p.Lys1026Ter	Homozygous	Nonsense	Nonreported	Likely pathogenic	SCID (T-B+NK-)
4	RFXANK	c.634C>T	p.Arg212Ter	Homozygous	Nonsense	Nonreported	Pathogenic	CID (MHC class II deficiency)
5	DOCK8	c.2206-2C>G (IVS19-3C > G)	-	Homozygous	Splicing	Nonreported	-	CID (DOCK8 deficiency)
6	DOCK8	c.3067_3068insTA	p.Val1024lfs*13	Homozygous	frameshift	Nonreported	Pathogenic	CID (DOCK8 deficiency)
7	DOCK8	c.3067_3068insTA	p.Val1024lfs*13	Homozygous	frameshift	Nonreported	Pathogenic	CID (DOCK8 deficiency)
8	DOCK8	Exon 1 deletion	-	Homozygous	Deletion	Nonreported	Pathogenic	CID (DOCK8 deficiency)
9	PNP	c.349G>A	p.Ala117Thr	Homozygous	missence	Nonreported	VUS	CID (PNP deficiency)
10	PNP	c.349G>A	p.Ala117Thr	Homozygous	missence	Nonreported	VUS	CID (PNP deficiency)
11	CORO1A	1191_1192insC	p.Ser401fs	Homozygous	frameshift	Nonreported	Pathogenic	CID (CORONIN1A deficiency)
12	CORO1A	1191_1192insC	p.Ser401fs	Homozygous	frameshift	Nonreported	Pathogenic	CID (CORONIN1A deficiency)
13	TAP1	c.1312C>T	p.Arg438Ter	Homozygous	Nonsense	Reported	Pathogenic	CID (MHC class I deficiency)
14	RAG1	c.1438A>G	p.Ser480Gly	Homozygous	missence	Reported	VUS	CID (RAG1 deficiency)
15	TTC7A	c.1037T>C	p.Leu346Pro	Homozygous	missence	Reported	Pathogenic	CID (TTC7A deficiency)
16	DCLRE1C (Artemis)	c.194C>T	p.Thr65Ile	Homozygous	missence	Reported	Pathogenic	CID (DCLRE1C deficiency)
17	ARPC1B	c.500+2T>C	-	Homozygous	Splicing	Nonreported	Likely pathogenic	CID (ARPC1B deficiency)
18	ARPC1B	c.613_614dup	p.His206TyrfsTer16	Homozygous	Splicing	Nonreported	Likely pathogenic	CID (ARPC1B deficiency)

ACMG: The American College of Medical Genetics and Genomics CID: combined immunodeficiency SCID: severe combined immunodeficiency VUS: variant of unknown significance

Table 8. Survival of patients based on diagnosis and HSCT

	Diagnosis (n)	Alive	Died	HSCT	Alive after HSCT	Died after HSCT
SCID	T-B-NK+ (14)	6	8	8	6	2
	T-B+NK+ (7)	2	5	2	2	-
	T-B+NK- (2)	-	2	-	-	-
CID	MHC class 2 deficiency (9)	2	7	2	1	1
	DOCK8 deficiency (6)	3	3	4	3	1
	Omenn syndrome (4)	1	3	2	1	1
	PNP deficiency (3)	1	2	1	1	-
	ARPC1B deficiency (2)	-	2	-	-	-
	Coronin1Adeficiency (2)	2	-	-	-	-
	TTC7A deficiency (1)	-	1	-	-	-
	Complete DiGeorgesyndrome(1)	1	-	-	-	-
	RAG1 deficiency(1)	1	-	-	-	-
	MHC class 1deficiency (1)	1	-	-	-	-
	DCLRE1C deficiency (1)	1	-	1	1	-

Early diagnosis of patients with SCID is crucial for early HSCT and improved survival rates. However, delays in diagnosis are common as clinicians are often unaware of the condition. The only factor that alerts clinicians to consider SCID is a positive family history (22). Similarly, in our cohort, only one patient was diagnosed without presenting symptoms as they had a sibling who had died from SCID before symptoms appeared.

Although the exact incidence of SCID has not been documented in our country, the high rate of consanguineous marriages poses a significant risk. In our cohort, the rate of consanguinity was 77.8%, and the rate of family history of the disease was 44.4%. Previous reports from our country, also indicate similarly high rates of consanguinity (5, 14, 23, 24).

Lymphopenia is an important diagnostic indicator of SCID. An absolute lymphocyte count below 3,000/mm^3 in patients under one year and 1,500/mm^3 in patients over one year is indicative of lymphopenia. In our study, the median lymphocyte count was 640/mm^3 (100-4,190) in patients diagnosed with SCID, and 1,600/mm^3 (160-66,946) in patients diagnosed with CID. In the study by Korkmaz *et al*. (12) the mean lymphocyte count in all patients was 1489/mm^3 (100-9,200/mm^3). The mean lymphocyte count was 1,505/mm^3 (100-9,200/mm^3) in patients admitted under one year of age (n=58) and 1378/mm3 (200-3,400/mm^3) in patients admitted between 1 and 2 years of age (n=9). Therefore, the study emphasized that in countries where the rate of consanguineous marriage is high and AR inherited IEIs are common, the number of unrecognized patients can be minimized by considering a lower limit of lymphocyte count as 3000/mm^3 until the age of two years (12). Lymphopenia was detected in 90.9% of patients with SCID and 51.6% of patients with CID in our study. Reports from Turkey have shown that 86-95% of SCID patients have lymphopenia (12, 14). Similarly, studies reported lymphopenia in 85-95% of patients with combined immunodeficiency (21). Clinicians should be vigilant for lymphopenia and conduct additional immunological studies in patients with recurrent infections and lymphopenia.

The genetic defects identified in our cohort showed autosomal recessive inheritance. Variants compatible with clinical and laboratory data were detected in 18 patients who underwent genetic analysis, 9 of whom have not been reported before. Mutations in *TRAC*, *JAK3*, *RFXANK*, *DOCK8*, *PNP,*

CORO1A, *TAP1*, *RAG1*, *TTC7A*, *DCLRE1C* and *ARPC1B* genes were found in our patients. In a previous study in Turkey, Erman *et al*. (25) made a genetic diagnosis in 6 of 19 SCID patients. They discovered four new disease-causing mutations in the genes *RAG1, JAK3 and IL2RG*, respectively. Firtina *et al.* (13) found 24 disease-causing variants in 23 out of 38 SCID patients. The most common variants were detected in nine genes linked to SCID: *RAG1*, *RAG2, ADA*, *DCLRE1C*, *NHEJ1*, *CD3E*, *IL2RG*, *JAK3*, and *IL7R*.

HSCT is a curative treatment used in patients with SCID and CID (1, 2). In our cohort, 10 out of 23 (43.4%) SCID patients and 10 out of 31(32.2%) CID patients underwent HSCT totaling 20 out of 54 patients (37%). In two separate studies from Turkey, Akar *et al.* (23) found that 8 out of 40 (20%) SCID/CID patients and Bayram *et al*. (14) found that 61 out of 72 (85%) SCID patients underwent HSCT. Yao *et al*. (21) and Aluri *et al*. (26) reported that HSCT was undergone by 6 out of 44 (13.6%) and 4 out of 57 (7%) SCID patients, respectively. Finally, in the study by Rozmus *et al.* (27), 15 out of 40 (37.5%) SCID patients underwent HSCT, which is similar to our study. In our study, survival after HSCT was 80% (8 out of 10) for SCID patients and 70% (7 out of 10) for CID patients 8 (75% of all patients). Conversely, all patients with SCID who could not undergo HSCT died. Additionally, 21 CID patients could not undergo HSCT resulting in only 6 patients surviving (28.5%). When analyzing studies in the literature that evaluated patients with SCID and CID together, it was found that survival after HSCT was very low in studies conducted in India and China. In the study conducted in India, all patients who underwent transplantation were lost, while only one patient in China survived (21, 26). Two different studies, one from Turkey and one from Canada, reported survival rates after HSCT of 67.5% and 80%, respectively, which were similar to the results of our study (23, 27). In a multicenter study by Ikinciogullari *et al*. involving 234 patients with SCID who underwent HSCT between 1994 and 2014, the overall survival rate was 65.7% over a 20-year period (28). In a single center study by Bayram *et al*. involving 72 patients with SCID who underwent HSCT between 1997 and 2017, the overall survival rate was 80.3% over a 20-year period (14).

Early recognition of SCID and CID, as well as early HSCT are critically important (1, 2). If HSCT is performed within the first 3 months after diagnosis, the chance of success increases to 95 (28). In order to perform HSCT before 3.5 months, all patients should be diagnosed early, and this will only be possible with newborn screening programs. Early diagnosis through a screening program after birth will protect patients from life-threatening infections and internal organ damage and increase the success of HSCT. Severe combined immunodeficiency screening was included in the National Neonatal Screening Program in the United States in 2010 (29). Efforts on this subject are also ongoing in Turkey.

Although retrospective, the analysis of patients with SCID and CID combined with detailed genetic results is the strength of this report.

In conclusion, in countries where newborn screening data is not available, it is crucial to prioritize the detection of SCID patients to ensure early diagnosis and prevent treatment delays. Questions about consanguineous marriage, sibling deaths, and family members showing similar characteristics should be asked, leading to further investigations if lymphopenia is present. Timely recognition of lymphopenia and its associated symptoms is essential for early diagnosis and the successful implementation of curative HSCT treatment, thus preventing the onset of life-threatening infections. With the increasing number of genetic diagnosis facilities and HSCT centers the survival rate of patients also is expected to rise. Furthermore, educational activities should be conducted to enhance physicians' awareness of the disease.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Kliegman RM, Stanton BF, St Geme JW, Schor NF, Behrman RE. Nelson Textbook of Pediatrics 21st Edition. In: Buckley RH, Sullivan KE. Immunology, Part XIII, Severe Combined Immunodeficiency. Philadelphia: 2019. p.1097-1169
2. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010;125:S182-194
3. Murguia-Favela L, Min W, Loves R, Leon-Ponte M, Grunebaum E. Comparison of elapegademase and pegademase in ADA-deficient patients and mice. Clin Exp Immunol, 2020, 200.2:176-184
4. Cirillo E, Giardino G, Gallo V, D'Assante R, Grasso F, Romano R, et al. Severe combined immunodeficiency--an update. Ann N Y Acad Sci. 2015;1356:90-106
5. Yorulmaz A, Artaç H, Kara R, Keleş S, Reisli İ. Primer immün yetmezlikli 1054 olgunun retrospektif değerlendirilmesi. Astım Alerji İmmünoloji. 2008;6:127-134
6. Kutukculer N, Gulez N, Karaca NE, Aksu G, Berdeli A. Novel mutations and diverse clinical phenotypes in recombinase-activating gene 1 deficiency. Ital J Pediatr. 2012, 38.1:1-7.
7. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al; The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. ESID Registry Working Party and collaborators. J Allergy Clin Immunol Pract. 2019;7:1763-1770.
8. Aksu G, Genel F, Koturoglu G, Kurugol Z, Kutukculer N. Serum immunoglobulin (IgG, IgM, IgA) and IgG subclass concentrations in healthy children: a study using nephelometric technique. The Turkish Journal of Pediatrics. 2005;47:19-24.
9. Ikinciogullari A, Kendirli T, Dogu F, Egin Y, Reisli I, Cin S, et al. Peripheral blood lymphocyte subsets in healthy Turkish children. The Turkish Journal of Pediatrics. 2004;46:125-30.
10. Kopanos C, Tsiolkas V, Kouris A, Chapple CE, Albarca Aguilera M, Meyer R, et al. VarSome: the human genomic variant search engine. Bioinformatics. 2019;35:1978-1980.
11. Regent A, Kluger N, Berezne A, Lassoued K, Mouthon L. [Lymphocytopenia: etiology and diagnosis, when to think about idiopathic CD4(+) lymphocytopenia?]. Rev Med Interne. 2012;33:628-34.
12. Korkmaz SB, Karaselek MA, Aytekin SE, Tokgoz H, Reisli I, Guner S, et al. Retrospective analysis of patients with severe combined immunodeficiency and alternative diagnostic criteria: A 20-year single center experience. Int J Immunogenet. 2023;50:177-184
13. Firtina S, Yin Ng Y, Hatirnaz Ng O, Kiykim A, Aydiner E, Nepesov S, et al. Mutational landscape of severe combined immunodeficiency patients from Turkey. Int J Immunogenet. 2020;47:529-538
14. Bayram O, Haskologlu S, Bayrakoğlu D, Bal SK, Islamoglu C, Cipe FE et al. A. Single-Center Study of 72 Patients with Severe Combined Immunodeficiency: Clinical and Laboratory Features and Outcomes. J Clin Immunol. 2021;41:1563-1573
15. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? J Allergy Clin Immunol. 2010;126:602-610
16. Fazlollahi M, Pourpak Z, Hamidieh A, Movahedi M, Houshmand M, Badalzadeh M, et al. Clinical, laboratory and molecular findings of 63 patients with severe combined immunodeficiency: a decade's experience. J Investig Allergol Clin Immunol. 2017;27:299-304
17. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, et al. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol. 2006;26:519-532.
18. Cirillo E, Cancrini C, Azzari C, Martino S, Martire B, Pession A, et al. Clinical, Immunological, and Molecular Features of Typical and Atypical Severe Combined Immunodeficiency: Report of the Italian Primary Immunodeficiency Network. Front Immunol. 2019 13;10:1908
19. Heimall J, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck JM, et al. Immune reconstitution and survival of 100 SCID patients post hematopoietic cell transplant: a PIDTC natural history study. Blood. 2017;130 :2718-2727
20. Luk ADW, Lee PP, Mao H, Chan K-W, Chen XY, Chen T-X, et al. Family history of early infant death correlates with earlier age at diagnosis but not shorter time to diagnosis for severe combined immunodeficiency. Front Immunol. 2017;8:808
21. Yao C-M, Han X-H, Zhang Y-D, Zhang H, Jin Y-Y, Cao R-M, et al. Clinical characteristics and genetic profiles of 44 patients with severe combined immunodeficiency (SCID): report from Shanghai, China (2004–2011). J Clin Immunol. 2013;33 :526-539

22. McWilliams LM, Railey MD, Buckley RH. Positive family history, infection, low absolute lymphocyte count (ALC), and absent thymic shadow: diagnostic clues for all molecular forms of severe combined immunodeficiency (SCID). J Allergy Clin Immunol Pract. 2015;3:585-591.
23. Akar HH, Patiroglu T, Hershfield M, van der Burg M. Combined immunodeficiencies: twenty years experience from a single center in Turkey. Cent Eur J Immunol. 2016;41:107-115
24. Kilic SS, Ozel M, Hafizoglu D, Karaca NE, Aksu G, Kutukculer N. The prevalences [correction] and patient characteristics of primary immunodeficiency diseases in Turkey--two centers study. J Clin Immunol. 2013;33:74-83.
25. Erman B, Bilic I, Hirschmugl T, Salzer E, Boztug H, Sanal Ö, et al. Investigation of Genetic Defects in Severe Combined Immunodeficiency Patients from Turkey by Targeted Sequencing. Scand J Immunol. 2017;85:227-234
26. Aluri J, Desai M, Gupta M, Dalvi A, Terance A, Rosenzweig SD, et al. Clinical, immunological, and molecular findings in 57 patients with severe combined immunodeficiency (SCID) from India. Front Immunol. 2019;10
27. Rozmus J, Junker A, Thibodeau ML, Grenier D, Turvey SE, Yacoub W, et al. Severe combined immunodeficiency (SCID) in Canadian children: a national surveillance study. J Clin Immunol. 2013;33:1310-6.
28. Ikinciogullari A, Cagdas D, Dogu F, Tugrul T, Karasu G, Haskologlu S, et al. Turkish Pediatric Bone Marrow Transplantation Sub Group (TPBMT-SG). Clinical Features and HSCT Outcome for SCID in Turkey. J Clin Immunol. 2019;39:316-323
29. Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency neonates: the winner is T-cell receptor excision circles. J Allergy Clin Immunol. 2012;129:607-616