Consanguinity Rate and Delay in Diagnosis in Turkish Patients with Combined Immunodeficiencies: a Single-Center Study

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Abstract Combined immunodeficiency diseases comprise a group of disorders with different molecular basis. Clinical and immunological phenotypes for each group are extremely heterogenous. The frequency of combined immunodeficiencies may vary in different countries. The most frequent forms of combined immunodeficiency show inherited defects in development of T and/or B lymphocytes. These defects are classified according to immunologic phenotype and are categorized into T−B+ or T−B− including forms with or without natural killer lymphocytes. We report here twenty-three patients (female/male: 12/11) with combined immunodeficiency showing different immunological and clinical phenotypes, majority of whom were admitted because of severe upper and lower respiratory tract infections. Mean age of the study group, mean age at onset of the symptoms, and diagnosis were 47.5±42.2, 11.2±17.3, and 19.5±23.8 months, respectively. There was nearly 8 months time delay between beginning of symptoms and diagnosis. Within the combined immunodeficiency phenotypes, T−B−NK+ category was the most frequent phenotype. Consanguinity was positive in 73.9% ($n=17$) of patients while it was about 80.0% ($n=8$) in deceased ten children. Bone marrow or umblical cord stem cell transplantation was applied to 11 of them. Three patients deceased after transplantation and seven patients deceased without transplantation. Twelve patients are being followed by prophylactic treatment. In conclusion; combined immunodeficiencies are frequent in our country because of high rate of consanguinity. T−B− combined immunodeficiencies are more often observed, and infants presenting severe infections beginning in the first 3 months of life have to be examined for combined immunodeficiencies. Shortening of time delay in diagnosis will increase success of life-saving treatment.

Keywords CID · immunodeficiency · consanguinity

Abbreviations
CID   Combined immunodeficiency diseases
SCID   Severe combined immunodeficiency diseases
RAG   Recombination activating gene
IUIS   International Union of Immunological Societies

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Introduction

Defects in adaptive immune responses result with antibody deficiency syndromes and combined immunodeficiency diseases (CID). CID comprise a group of disorders with different molecular basis. Clinical and immunological phenotypes of different CID are extremely heterogenous [1]. In the last decade, advances in characterization of molecular mechanisms helped us in diagnosing patients

with early-onset infections and guided for selection of adequate treatment.

Recently, International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies reported an updated CID classification with 19 categories [2]. The most frequent forms of CID show inherited defects in development of T and/or B lymphocytes. These defects are classified according to immunologic phenotype and are categorized into T−B+ or T−B− including forms with or without natural killer lymphocytes. Mutations in any of known genes: IL2RG, Artemis, RAG1–2, ADA, CD45, JAK3, and IL7R cause severe combined immunodeficiency diseases (SCID). Defects in IL-dependent T and NK cell differentiation caused by mutations in the γc gene or the γc-associated Jak-3 kinase gene result in the T−B+NK− SCID phenotype. Deficiency of the α chain of the IL-7 receptor of CD45 and the CD3 chains accounts for the T−B+NK+ type of SCID phenotype. Defects in recombination activating gene 1 (RAG1) and RAG2 or Artemis gene can disrupt V(D)J recombination. So, blocked differentiation of T and B cells causes T−B−NK+ form of SCID. However, various RAG1/RAG2 mutations have been found to be associated with a spectrum of immunodeficiencies extending from T–B–NK+ SCID to Omenn syndrome. A new type of radiosensitive T−B−NK+ SCID with a defect in DNA ligase IV (LIG4) has been described to cause T−B−NK+ SCID without developmental defects as well as LIG4 syndrome, which was previously described and associated with chromosomal instability, pancytopenia, and developmental and growth delay. This LIG4-deficient SCID patient had an incomplete but severe block in precursor B cell differentiation, resulting in extremely low levels of blood B cells [3]. DNA-PKcs mutations in radiosensitive T−B− SCID patients inhibit Artemis activation and nonhomologous end-joining [4]. Cernunnos/XLF in this pathway may cause a leaky SCID phenotype [5]. The gene encoding the mitochondrial energy metabolism enzyme adenylate kinase 2 is mutated in individuals with reticular dysgenesis, the most severe form of inborn SCID [6]. Mutations in unidentified genes may also cause SCID. Population-based genotype and allelic frequencies of these gene defects have not been measured [7].

Various categories of primary immunodeficiencies are diagnosed in different countries indicating a wide ethnic and geographical variation [8–12]. In contrast to other countries, CID is previously reported as the most frequent in Turkish population in Northwestern Iran [13] and showed higher frequency in Egypt [14], Saudi Arabia [9], and in those countries with high consanguinity rate. The aim of this study was to review clinical, immunological, and molecular records of Turkish CID patients admitted to one of the Pediatric Immunology Departments in western region of the country and to draw attention to the importance of early diagnosis so as to prevent consanguineous marriages.

Patients and Methods

Twenty-three patients with CID who were admitted because of severe upper and lower respiratory tract infections and diagnosed during the period from 1998 to 2010 in Ege University Faculty of Medicine, Department of Pediatric Immunology, Izmir, Turkey were reviewed in this study. An evaluation sheet was used to summarize patients' demographic information including name, gender, date of birth, age at onset of symptoms, age at diagnosis, family history and consanguinity, clinical symptoms, laboratory, and molecular data. The patients were diagnosed and classified according to both clinical and laboratory criteria of CID reported by IUIS Expert Committee on Primary Immunodeficiencies [2]. Laboratory investigations performed for our patients included complete blood count with peripheral blood smear evaluation, serum immunoglobulins by nephelometry (Dade Behring BNII Nephelometer Analyzer, Germany), and lymphocyte phenotype (T, B, and NK cells) by flow cytometry (FACSCalibur, Becton-Dickinson, USA). Genetic testing was performed in different European Laboratories and also in Pediatric Molecular Analysis Laboratory of Ege University (acknowledgement).

Statistical analyses were performed using SPSS (Windows version 17.0, SPSS Inc., Chicago, IL).

Results

Characteristics of Patients

Twenty-three patients (F/M: 12/11) with CID showing different immunological and clinical phenotypes were reported. Mean age of the whole study group, mean age at onset of symptoms, and mean age at diagnosis were 47.5 ± 42.2, 11.2 ± 17.3, and 19.5 ± 23.8 months, respectively. There was nearly 8 months time delay between onset of symptoms and diagnosis.

Consanguinity was positive in 73.9% ($n=17$) of patients while it was about 80.0% ($n=8$) in deceased ten children. Eleven patients' (64.7%) parents were first-degree cousins. A positive family history of immunodeficiency was noticed in ten patients (43.5%). Eighteen patients (78.2%) presented severe infectious symptoms and 12 patients (52.1%) were diagnosed before the age of 1 year. Immunoglobulin concentrations prior to substitution therapy, lymphocyte subset percentages, and absolute lymphocyte counts are listed in Table I. Age-matched reference values are also provided [15, 16].

Table I Laboratory findings of patients with combined immunodeficiency

Laboratory parameters	SCID						Others		
(Age-matched reference values; Ref.no: 15,16)	T−B+NK− (n=3)	T−B+ NK+ (n=1)	T−B−NK+ (n=5)	T+B−NK+ (n=3)	T+B+NK+ (n=2)	Omenn syndrome (n=2)	MHC class II deficiency (n=2)	CD40 deficiency (n=4)	CD40 ligand deficiency (n=1)
IgG (mg/dl)[a] (774±199)	555.6±579.3	145	674±482	1677±264.6	874.5±1011	871±295.5	305.0±224.8	185.2±94.3	373
IgA (mg/dl)[a] (44±18)	4.93±2.55	25.4	7.78±4.03	824±118.5	30±31.1	27.5±30.4	14.2±12.5	5.97±0.46	6.67
IgM (mg/dl)[a] (98±40)	27.6±10.4	16.8	56.1±88.2	133.6±82.4	63.5±16.2	97.5±115.2	62.3±60.3	796.9±862.2	118
WBC/mm³ (6000–11,000)	4690±2978	5350	4954±3337	6773±1706	13250±3181	21950±3889	4667±2393	12650±5779	4600
Abs. lymphocyte/mm³ (3400–6600)	1903±1189	1700	1057±792.3	2296±1350	6565±1506	7765±2292	2187±2841	7325±6247	2760
CD3+% (62–69)	8±13	5	9.86±16.5	57.6±19.5	55.0±5.65	85.0±9.89	33.8±11.1	73.8±12.4	42
CD3 + CD4+% (29–51)	4.66±7.23	4	3.08±5.73	11.0±5.87	23.0±19.7	26.0±9.89	10.9±8.41	25.2±18.5	35
CD3+ CD8+% (16–33)	3.66±5.50	4	10.6±10.8	41.3±19.5	29.0±14.1	53.5±9.19	18.8±3.95	44.9±15.0	15
CD19+% (21–28)	66.3±24.5	83	0.62±1.27	2.26±2.66	33.0±4.24	0±0	57.3±16.5	17.3±11.9	40
CD3−CD16+56+NK cells% (4–15)	2.66±2.88	5	63.6±22.7	33.3±18.5	11.5±6.30	6.50±6.36	7.90±1.27	10.0±1.41	7
HLA DR+ T cell%[b] (7–15)	9.50±12.02	2	22.6±25.3	47.0±19.0	24.5±17.6	79.0±8.48	0.52±0.67	44.7±20.6	6

[a] Immunoglobulin levels are obtained at admission prior to substitution therapy

[b] % of T cells co-expressing HLA-DR (active T cells)

Distribution of Diseases

The frequency of immunological phenotypes and molecular results are shown in Table II. Within the CID phenotypes, the T−B−NK+ category was the most frequent phenotype. In the whole group, RAG1 mutation was frequent and confirmed with nine patients showing diverse phenotypes as Omenn Syndrome (n=2), T−B−NK+ SCID (n=3), T+B−NK+ SCID (n=2), and T+B+ K+ SCID (n=2).

Clinical Features

Patients presented a wide spectrum of incoming clinical presentations including chronic diarrhea (n=2), severe opportunistic infections (n=10), dermatitis (n=3), infections plus dermatitis (n=3), infections plus moniliasis (n=3), or all of them (n=4). The lower and upper respiratory tract diseases were the most frequent (n=20) infection types followed by chronic diarrhea. There was a total of five patients with T+B−NK+ and T+B+NK+ SCID. None of them had any clinical evidence of maternal T cell engraftment such as signs of graft-versus-host disease. Two of them were evaluated for chimerism by performing selective HLA typing of T cells and non-T cells and maternal T cell engraftment was not observed in both of them.

Mortality and Survival

Bone marrow or umblical cord stem cell transplantation was applied to 11 of them. These patients received bone marrow from siblings (n=5), haploidentical mother (n=3), haploidentical father (n=1), and matched unrelated (n=2) donor. Mean follow-up duration after transplantation was 17.7±8.5 months (min 7, max 36). Three patients deceased after transplantation and seven patients deceased without transplantation. Twelve patients are being followed by prophylactic intravenous immunoglobulin (IVIG) replacement treatment.

Discussion

Epidemiological studies have shown wide geographical and racial variations in terms of prevalence and pattern of immunodeficiency. Many countries worldwide have developed registries to estimate the prevalence and characteristics of different primary immunodeficiency phenotypes among their populations [14]. In Middle East countries, frequency of CID is higher than western countries. This could be due to geographical, ethnic, and genetic predisposition in this region. In western countries, severe combined immunodeficiencies have a prevalence of approximately 1:50,000 live births and

Table II Immunological phenotype and molecular analysis results of patients with combined immunodeficiency

Diseases	n	Age (months)	Gender (F/M)	Age at onset of symptoms (months)	Positive consanguinity (n)	Molecular analysis (n)	Positive autoimmunity (n)	BMT (n)	Follow-up (n)	
									Ex	IVIG
T−B+NK−	3	70.6±59.0	1/2	1.66±1.04	1	No known mutation was detected (1) JAK3: homozygous mutation exon2 322_324 del TTC, effect F88 del (2)	1	2	1	2
T−B+NK+	1	26	0/1	7.0	1	Probable diagnosis: IL7Rα defect (1) (No molecular analysis could be performed)	–	1	1	–
T−B−NK+	5	16.1±11.3	5/0	3.40±1.29	4	No molecular analysis could be performed (2) RAG1: p.R394Q/p.R394Q homozygous mutation (2) RAG1: p.R776Q, 3047–3049 del GCC (1)	–	3	3	2
T+B−NK+	3	84.6±55.9	1/2	15.0±14.7	2	No known mutation was detected (1) RAG1: p.H249R/p.K820R heterozygous mutation (2)	2	–	1	2
T+B+NK+	2	49.0±4.24	1/1	2.75±0.35	2	No molecular analysis could be performed (1) RAG1: k242fsX246 (1)	–	2	0	2
Omenn syndrome	2	8.50±9.19	1/1	0.62±0.53	0	RAG1: p.H249R heterozygous mutation (1) RAG1: p.Q248X/p.Q248X homozygous mutation (1)	–	–	1	1
MHC class II deficiency	2	42.5±45.9	0/2	12.5±7.77	2	RFXANX gene mutation (1) No molecular analysis could be performed (1)	–	2	1	1
CD40 deficiency	4	77.7±36.5	3/1	37.0±28.3	4	IVS3-2A > T, homozygous mutation at acceptor splice of intron 3 (1) I33fsX48 (1) c.755_758 del AGGA (2)	1	2	1	2
CD40 ligand deficiency	1	11	0/1	6.0	1	p.E202X (1)	–	–	1	–

are more common in male subjects [1, 17]. In our study group, gender distribution was nearly (F/M:12/11) the same. Shabestari et al. [13] performed a study in order to find the frequency of primary immunodeficiencies (PID) in Turkish ethnic group of Northwestern Iran. The estimated occurence of PID is about 24 per 100,000 live births in this region. Combined T- and B-cell immunodeficiencies were the most common form of PID in this region, including severe combined immunodeficiency (32.2%), followed by ataxia-telangiectasia (22.0%) and common variable immunodeficiency (18.6%). In a Turkish study performed in Konya, a city in central Turkey, the occurence of SCID was found to be four per 40,000 live births [18].

In our study, the mean age at onset of symptoms was (11.2±17.3 months) under 1 year. Twelve patients (52.1%) were diagnosed before 1 year of life. There was nearly 8 months time delay between the beginning of symptoms and diagnosis similar to studies by Al-Herz et al. (7.5 months) [10] and Reda et al. (6.6 months) [14]. This period will only be shortened if the clinicians' awareness on primary immunodeficiencies in case of recurrent infections in early life increases. This is very important for the selection of early and adequate treatment.

Consanguinity rate was high (73.9%; n=17) similarly in other reported studies in Middle East countries [9, 10, 13]. First-degree-cousin marriage was 64.7% (n=11) and so, a positive family history was detected with ten patients (43.5%). High rate of consanguineous marriages is a social and health problem in our country caused by unsatisfactory education and traditional concepts. According to recent data,

rate of consanguineous marriages is 21%. Educational and social programs have to be done countrywide by government.

Although X-linked SCID is the most common form of CID worldwide [1], within the CID phenotypes in our study group, T−B−NK+ category was the most frequent phenotype. In Yorulmaz et al's study [18], 10/25 (40%) of SCID patients were T−B−NK+ SCID which was followed by 4/25 (16%) T−B+NK− and 4/25 (16%) T−B+NK+ SCIDs.

In the whole group, RAG1 mutation was frequent and has been found to be associated with a spectrum of immunodeficiencies extending from T−B−NK+ SCID to Omenn syndrome with nine patients. In approximately 70% of T−B−NK+ patients, mutations are found in RAG1 and 2 gene and the remaining show mutations in Artemis and LIG4 gene in literature [3, 19, 20]. In our patients with T−B− SCID phenotype, RAG1 gene mutation was frequent (n=3), while Jak 3 gene defect (n=2) and IL7R α gene defect (n=1) were responsible for T−B+ SCID. We have previously reported two SCID patients with hypomorphic mutations in RAG1 gene presenting distinct clinical spectrums [21].

Omenn syndrome is a rare CID characterized by the presence of a substantial number of oligoclonal, activated T cells, and the lack of B lymphocytes, associated with particular clinical features such as generalized erythroderma, lymphadenopathy, hepatosplenomegaly, and increased occurrence of life-threatening infections [22]. Both of our two patients with Omenn syndrome were admitted very early in life (0.5 and 2.5 months, respectively), presenting severe respiratory tract infections. Within medical history, there was no consanguineous marriage, and one of them died prior to transplantation.

We diagnosed two patients with major histocompatibility complex (MHC) class II deficiency which is more common in certain geographic regions as North Africa [1]. One of them died before transplantation at the age of four and the other living patient had just practiced with bone marrow transplantation (BMT) from matched unrelated donor by the time of this study.

Inadequate interactions between CD40 and CD40 ligand (also called as CD154) result with HIGM syndromes characterized by recurrent bacterial and opportunistic infections associated with decreased serum levels of IgG, IgA, and IgE, and normal to increased serum levels of IgM [23]. Patients with CD40 or with CD40L deficiency share a common and severe phenotype similar to SCID patients. Increased susceptibility to infection is the hallmark of X-linked hyper-IgM (XHIGM) syndrome, while most patients usually develop symptoms of combined immunodeficiency in their first year of life [24]. Our one X-HIGM patient was symptomatic at the age of 6 months and died after 5 months. Three of four CD40 deficient patients are stil living and two of them are receiving IVIG therapy and waiting in the BMT list. One of these three living patients that was diagnosed in our department was the first patient in the literature that thereafter successfully practiced with BMT in Brescia, Italy and recovered completely without need for immunoglobulin replacement therapy [25].

Patients with CID present recurrent opportunistic infections early in life. Our patients showed a spectrum of incoming manifestations including chronic diarrhea, severe opportunistic infections, dermatitis, moniliasis, or all of them. The lower and upper respiratory tract diseases were the most frequent infection types followed by chronic diarrhea.

The survival of SCID patients after birth is dependent on some factors such as early diagnosis and the availability of appropriate medical care and treatment. Because SCID may be unrecognized, with infant deaths from infection attributed to other causes, so, newborn screening is the only way to ascertain true birth prevalence. In the study of Shabesteari et al. [13], the mortality rate in ethnic Turk region was 25%, which is much higher than other areas due to lack of developed methods of treatment for these patients. In our study group, bone marrow or umblical cord stem cell transplantation was applied to 11 patients and three patients deceased after transplantation. Mean follow-up duration after transplantation was 17.7 ± 8.5 months. Seven patients deceased without transplantation perhaps due to late diagnosis and inadequate treatment.

Although there is still no national registry in Turkey, we can claim that CIDs are frequent because of high rate of consanguinity especially in eastern regions. T−B− CIDs are more often observed and infants presenting severe infections

beginning in the first 3 months of life have to be examined for CIDs. Early diagnosis by increasing awareness of physicians about these disorders and educational programs for preventing consangineous marriages are quite important. Life-saving treatment and precautions can be implemented to decrease mortality and morbidity and to improve the quality of life.

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