Original Research

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Immunophenotype, Clinical Effect, and Comparison of TNFRSF13B/TACI Mutations: A Single-Center Retrospective Cohort Study of 34 Patients

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Abstract

Objective: In this study, the clinical and laboratory findings, complications, and responses to regular intravenous immunoglobulin (IVIG) treatment of 34 common variable immunodeficiency (CVID) patients with transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) mutation were evaluated retrospectively.

Materials and Methods: The clinical characteristics, immunological and laboratory findings of patients whose TACI mutation was detected by the next generation sequencing method and who were followed in our clinic with the diagnosis of CVID were examined.

Results: Of the patients, 20 (59%) were male and 14 (41%) were female. Eighteen patients were children (<18 years old) who had a median age of genetic diagnosis of 6.2 years and 16 were adults (>18 years) with a median age of genetic diagnosis of 34 years. The most common complaint was recurrent respiratory tract infection (68%). In 20 of the patients, lymphoproliferation and related lymphoproliferation, growth retardation, lymphoma, immune thrombocytopenic purpura, Hashimoto's thyroiditis, Crohn's disease, autoimmune neutropenia, Celiac disease, bronchiectasis, type 1 Diabetes, and asthma were observed. A statistically significant difference was detected between the lymphocyte values of pediatric and adult patients who had comorbidity and those that were not detected. According to the European Society of Immunodeficiencies/the Pan-American Immunodeficiency Group (ESID/PAGID), 16 patients who met the diagnostic criteria had significantly lower lymphocyte, immunoglobulin (Ig) A, IgG, naïve ($CD19^+IgD^+CD27^-$), non-switched cell ($CD19^+IgD^-CD27^+$) percentage than 18 patients who did not match. Of 34 patients, a total of 24, 13 of whom were children and 11 of whom were adults, received regular IVIG treatment because they met the criteria for ESID/PAGID and/or had comorbidities.

Conclusion: In our study, the fact that bronchiectasis and recurrent pneumonia and the need for hospitalized treatment were less common than in the literature was thought to be related to early IVIG treatment.

Keywords: TACI mutation, hypogammaglobinemia, common-variable immunodeficiency, autoimmunity, B and T-cell

Introduction

Innate immune defects (IIDs) constitute a large group of diseases that manifest clinically as a predisposition to infections, autoimmunity, autoinflammatory diseases, allergies, bone marrow failure, and/or malignancies. The largest patient group in the literature consists of those who have common variable immunodeficiency (CVID) (1). More than 480 monogenic defects causing primary immunodeficiency (PID) called IIDs have been identified recently (2). Next-generation sequencing, whole exome sequencing, or gene panels are generally employed in the genetic diagnosis of PID patients (3).

According to the diagnostic criteria of the European Society of Immunodeficiencies (ESID) and the Pan-American Immunodeficiency Group released in 1999, at least 2 major immunoglobulin levels (especially IgG and IgA and/or IgM levels) should be 2 SD of the levels determined by age in the diagnosis of CVID and the causes of hypogammaglobinemia should be excluded by finding symptoms after the age of 2 years. The International

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Consensus on Commonly Variable Immunodeficiency Disorders introduced novel criteria for the diagnosis of CVID in 2015 (4), which were revised by the ESID in 2020 (5).

Transmembrane Activator and Calcium Modulator and Cyclophilin Ligand Interactor (TACI) is a tumor necrosis factor superfamily member expressed on the surface of B lymphocytes and plasma cells as one of the receptors of B-cell activating factor and proliferation-inducing ligand (APRIL) (6,7). It also regulates B-cell homeostasis and function, and supports the IgG and IgA recombination in germinal center B-cells and the survival and differentiation of plasma cells (8,9).

The mutations in the *TNFRSF13B* gene that encodes TACI are detected in 7-10% of CVID patients (6,10), which was reported as 7.1% in our country (11). The most common mutations in patients with clinical symptoms were defined as C104R, A181E, C76R, and R202H (12).

The deactivation of the TNFRSF13B region results in a T-cell-independent impaired type II (TI-2) response and abolishes APRIL-dependent IgA, IgE conversion (13,14), which then causes lymphoproliferation and a fatal autoimmune syndrome (15). Salzer et al. (10) argued that the risk of developing autoimmunity was higher, especially in people with heterozygous C104R variants, compared to those who had homozygous mutations.

It is recommended to carefully follow up the symptoms of TACI patients regularly for autoimmunity, malignancy or possible complications and treat any infection with antibiotics along with intravenous immunoglobulin (IVIG) treatment (16).

The immunological and clinical characteristics of the patients, TACI mutation types, and response to IVIG treatment were compared in this single-center study that included 34 patients.

Materials and Methods

The approval of the Ondokuz Mayıs University Faculty of Medicine Children's Hospital Ethics Committee was obtained for the study (approval no: 2022/447 date: 16.05.2023). Participating patients and their relatives were informed and consent forms were obtained.

The demographic data, family history, clinical findings, developing complications (malignancy, lymphoproliferation, ITP, etc.), complete blood count and the serum immunoglobulin levels absolute lymphocyte counts and subgroups (naive, non-switched memory, switched memory B-cells), age at diagnosis and accompanying comorbidities of 34 patients who applied to Ondokuz Mayıs University Faculty of Medicine, Department of Pediatric Immunology-Allergy between January 2017 and December 2021 were evaluated retrospectively. Flow-cytometric analyses were performed via the Becton Dickinson 12-color BD FASCSLyrıc analysis program, immunoglobulin values were studied with the nephelometric method in the BN2 system in the plasma and they were compared with the literature data of healthy aged-matched children. Computed tomography, chest radiography, and other genetic examination results were also evaluated. The TACI mutations of the patients were determined in the Department of Genetics with the 200-Gene Next-Generation Primary Sequencing Method within the scope of the immunodeficiency panel.

The laboratory results of patients under 16 years of age and over 16 years of age were compared with healthy reference values.

Statistical Analysis

The Independent Sample t-tests, Mann-Whitney test, Fisher's Exact test and Continuity Correction test were used for demographic comparisons, complications, lymphocyte subgroups and response to treatment.

Results

A total of 20 (58.8%) of the patients were male and 14 (41.1%) were female; 7 pediatric patients were girls (39%), 11 were boys and the mean age at the onset of symptoms was 6.5 ± 5.1 (median 2.5) years, the mean age of genetic diagnosis was 7.6 ± 5 (median 6) years. Five of the adult patients were female, 11 were male, the mean age of onset of complaints was 44 ± 14 years, and the mean age of genetic diagnosis was 34.8 ± 11.5 years. Among the patients, 32 (94.1%) were heterozygous and 2 (5.9%) were homozygous (>18 years old, c.61+1G>A and C104R). Eigth (23.5%) patients were siblings of consanguineous marriage and 19 (55.8%) had a family history. The disease demographic data are presented in Table 1.

C104R mutation was detected in 16 patients (6 children, 10 adults). The variants of uncertain significance were detected more frequently in children of uncertain significance were detected more frequently in children (66.7%) (p=0.47). The distributions of mutations are indicated in Figure 1.

The data of 19 patients from 9 families with a family history are presented in Table 2. Medical history of the patients revealed that only two of them (46 and 12 years old) had no problems and the others required immunological evaluation.

The initial complaint of the patients was related to respiratory tract diseases (2 bronchiectases, 5 pneumonia, 4 asthma), abdominal pain in 12 (35%), and joint pain in 4 (11.8%) patients (68.0%). Other complaints were rash, anal abscess, impetigo, oral aphthae, and diarrhea (Figure 2).

Table 1. The demographic characteristics of the patients who have TACI mutation

Gender	Male	14	41%
	Female	20	59%
Consanguinity	Yes	8	24%
	No	26	76%
Family history of PID	Yes	15	44%
	No	19	56%
Children		Mean ± SD (years)	Min-Max (years)
Onset age of complaints (years)	Male	6.5 ± 5.1	0.03-16
	Female	6.6 ± 5.3	0.2-15
Age of diagnosis	Male	8.3 ± 5.2	1-16
	Female	6.7 ± 4.8	1-14
Mutation state	Heterozygous	18	53%
Adults		Mean ± SD (years)	Min-Max (years)
Onset age of complaints (years)	Male	44.3 ± 14	44 ± 19.7
	Female	34.8 ± 11.5	45 ± 0
Age of diagnosis	Male	34.8 ± 13.4	19-59
	Female	34.8 ± 8.5	26-49
Mutation state	Heterozygous	14	41%
	Homozygous	2	5.8%

TACI: Transmembrane activator and calcium modulator and cyclophilin ligand interactor, SD: Standard deviation, Min-Max: Minimum-Maximum, PID: Primary immunodeficiency

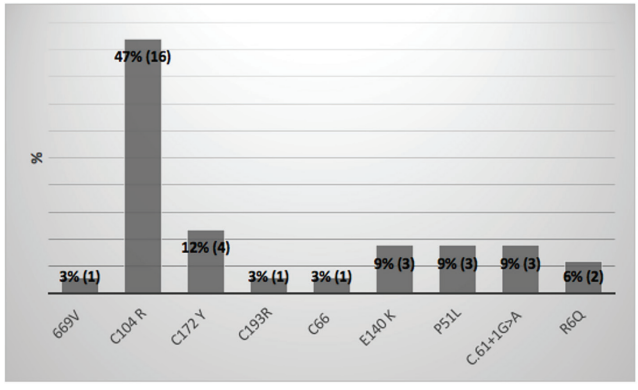

Figure 1. Distribution of mutations.

Four patients (11.7%) had asthma and recurrent urticarial attacks were observed in 3 patients (8.8%). The mean Ig E value of these patients was found to be 306.5 IU/mL and the eosinophil count was 160 IU/mL.

Gastrointestinal symptoms were detected in 12 patients (5 with diarrhea). Upper gastrointestinal system endoscopy was performed on 3 patients, 2 had mild villous atrophy and mononuclear cell infiltration, and one had inflammatory bowel disease.

Low serum IgA was detected in 5 patients (3 adults in 2 children). Four (11.7%) patients had selective IgA

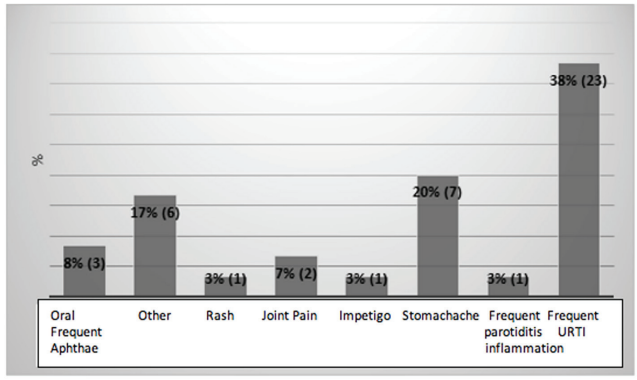

Figure 2. The initial admission complaints of the patients.
URTI: Upper respiratory tract infection

deficiency and 1 patient (3.0%) had partial IgA2 deficiency. Tests were not taken from two people who did not have any complaints. Six patients (8.8%) had serum IgM values above the reference range (3 children, 3 adults).

Of levels 20 patients who had growth retardation, lymphoma, immune thrombocytopenic purpura (ITP), Hashimoto's thyroiditis, Crohn's disease, autoimmune neutropenia, celiac disease, bronchiectasis, and type 1 diabetes comorbidities, 9 (45.0%) were children and 11 (55.0%) were adult. Lymphoproliferation (LAP, splenomegaly, hepatomegaly) improved in 6 patients (2 children, 4 adults) (Tables 3 and 4). A statistically significant difference was detected between the absolute lymphocyte values of patients who had comorbidity and those that were not detected (p=0.013). In lymphocyte subgroups, the percentages of CD8, $CD3^+CD56^+$, non-switched ($CD19^+IgD^+CD27^+$), switched ($CD19^+IgD^-CD27^+$) memory B-cells were found to be low, but no statistical difference was detected (Table 5).

Of levels 16 patients (47%) who fully met the ESID diagnostic criteria for CVID, 9 were male and 7 were female. Accordingly, in all age groups, the lymphocyte (p=0.005), serum IgA (p=0.02) and serum IgG (p=0.0004) levels were statistically lower than the patients who did not fully cover CVID criteria**.** The CD4/CD8 ratio of patients who fully met the criteria was found to be 1.6 ± 0.67, but there was no statistical difference (p=0.25). White blood cells (p=0.78), CD3 (p=0.84), CD8 (p=0.48), IgM (p=0.78), switched memory B-cell (p=0.85) were found to be numerically and proportionally lower in children and adults who met the CVID diagnostic criteria when compared to the patients who did not meet the criteria. However, numbers of non-switched B-cells ($CD19^+IgD^+CD27^+$) (p=0.45) and naïve ($CD19^+IgD^+CD27^-$) B-cells (p=0.8) were found to be higher (Table 6). Immunological values of patients meeting CVID criteria were indicated in Table 7.

Lymphocyte subgroups, immunoglobulins and lymphocyte subgroup in populations patients who met and

Table 2. The data of 19 patients from nine families with a family (parent) history

Family	Individual	Age	Clinic	Mutation	Gender	Serum IgG (g/L)	Serum IgA (g/L)	Serum IgM (g/L)
A	I	6	Frequent Parotitis, Frequent URTI	C104R	M	4.5 (9.1-11.1)	0.58 (0.9-1.2)	0.49 (1-1.3)
	II	18m	Frequent URTI	C104R	F	4.6 (6.7-8.5)	0.18 (0.3-0.5)	0.55 (1-1.4)
B	I	30m	Frequent URTI, impetigo lymphadenopathy Abdominal tuberculosis	C104R	F	6.7 (7.1-9)	0.3 (0.5-0.7)	1 (0.9-1.2)
	II	26	Frequent URTI, folliculitis appendectomy	C104R	F	10.3 (11-14)	0.8 (1.6-2.3)	1.1 (1.1-1.6)
C	I	10	ITP, frequent URTI	P51L	M	16.5 (9.3-11.7)	0.06 (0.9-1.3)	1.1 (0.9-1.2)
	II	46	None	P51L	M			
	III	12	None	P51L	M			
D	I	9	Pneumonia, eczema, pericarditis	E140K	M	8.6 (9.3-1.1)	0.8 (0.9-1.1)	1.1 (9.6-1.3)
	II	19	Splenomegaly Hashimoto Adenoidectomy	E140K	M	11 (9.3)	0.69 (0.9-1.3)	0.62 (0.9-1.2)
	III	47	A*bdominal pain*	E140K	M	13.9 (11-14)	1.9 (1.6-2.3)	8.2 (1.1-1.6)
E	I	1	Recurrent anal abscess	C172Y	M	3.74 (3.7-4.8)	0.06 (0.08-0.1)	0.25 (0.3-0.4)
	II	27	Frequent URTI	C172Y	F	13 (11-14)	5.4 (1.6-2.3)	0.08 (1.1-1.6)
F	I	2 m	Frequent URTI, Pneumonia	R6Q	F	2.75 (3.7-4.8)	0.11 (0.08-0.12)	1.02 (0.3-0.4)
	II	14	Celiac type 1 DM	R6Q	F	10.4 (10.6-12)	1.56 (0.9-1.7)	1.79 (1.1-1.4)
G	I	35	Frequent URTI Splenomegaly	c.61+1G>A	M	5.4 (11-14)	0.08 (1.6-2.3)	0.3 (1.1-1.6)
	II	3	Adenoidectomy Tonsillectomy	c.61+1G>A	M	4.9 (7.7-9)	0.4 (0.5-0.8)	0.5 (1-1.3)
	III	6	None	c.61+1G>A	F	8.09 (9.2-11.1)	0.82 (0.9-1.2)	0.95 (1-1.3)
H	I	2	Frequent URTI Adenoidectomy	C104R	M	5.83 (7-9)	0.48 (0.4-0.7)	1.2 (0.9-1.2)
	II	58	None	C104R	M	10.9 (11-14)	1..42 (1.6-2.3)	0.74 (1.1-1.6)

URTI: Upper respiratory tract infection, ITP: Immune thrombocytopenic purpura, hom: Homozygote, m: Month. Reference ranges are indicated in parentheses, Ig: Immunoglobulin

Table 3. The mutation and comorbidity distribution of the pediatric patients

	Age (years)	Mutation	Comorbidity
P1	14	C104R	Hodgkin lymphoma, growth retardation
P2	2	C104R	Benign lymphoproliferation
P3	16	P51L	ITP
P4	1	C172Y	Anal abscess, asthma
P5	11	E140K	Pericardial effusion, eczema, asthma, growth retardation
P6	3	c.61+1G>A	Adenoidectomy, tonsillectomy
P7	8	C104R	Adenoidectomy
P8	14	R6Q	Celiac disease, type 1 DM, neutropenia

DM: Diabetes Mellitus, ITP: Immune thrombocytopenic purpura

Table 4. Mutation and comorbidity distribution in adults

	Age (year)	Mutation	Comorbidity
P1	39	C104R	Hashimoto's thyroiditis, asthma
P2	34	C104R	ITP
P3	49	C104R	Non-Hodgkin lymphoma, HSM
P4	39	C104R	Crohn's disease, neutropenia
P5	26	C104R	Appendectomy
P6	*23*	C104R	Splenomegaly, ITP
P7	34	C104R	Bronchiectasis, segmentectomy
P8	25	C104R	Bronchiectasis, tonsillectomy
P9	35	c.61+1G>A	Splenomegaly, benign lymphoproliferation
P10	47	E140K	Benign lymphoproliferation
P11	19	E140K	Splenomegaly, adenoidectomy, Hashimato thyroiditis, benign lymphoproliferation, asthma
P12	19	C104R	Adenoidectomy

ITP: Immune thrombocytopenic purpura

Table 5. Comparison of the patients with the patients without comorbidities and within the group

	Lymphocyte	Naïve	Non-switched B-cell	Switched B-cell	CD4	CD8	$CD16^+CD56^+$
Patients with comorbidities (n=20)	2333 ± 1294	61.1 ± 26.3	15.2 ± 17.9	7.9 ± 8	39.0 ± 5.9	26.7 ± 7.6	10.1 ± 6.7
Patients without comorbidities (n=14)	3711 ± 1568	58.4 ± 28.7	16.2 ± 13.4	9.7 ± 8.4	36 ± 7.8	27.9 ± 7.8	11.4 ± 8.9
p	0.013	0.68	0.44	0.41	0.56	0.73	0.7

Table 6. Immunological analysis of patients who meet and do not meet ESID/PAGID diagnostic criteria for CVID

	Patients with CVID	Patients without CVID	p
WBC (mm^3)	7817 ± 2514	7600 ± 1980	0.78
Lymphocyte (mcL)	2780 ± 1300	3090 ± 1672	0.05
Ig G (g/L)	12.3 ± 3.3	4.8 ± 2.1	0.0004
Ig A (g/L)	1.5 ± 1.1	0.43 ± 0.3	0.02
Ig M (g/L)	1.95 ± 2.1	1.6 ± 1.3	0.78
CD3 %	65.1 ± 10	64.8 ± 7.9	0.84
CD8 %	28.2 ± 7.1	26.3 ± 8.2	0.48
Naïve %	58.7 ± 29	61 ± 28.5	0.8
Switch %	8.9 ± 8	8.4 ± 8.4	0.85
Non-switch %	13.1 ± 10.7	17.6 ± 19.3	0.45
Patient	18	16	

Immunological parameters of 2 patients were not evaluated. In 1 patient, only the lymphocyte subgroup test was examined, ESID/PAGID: European Society of Immunodeficiencies/the Pan-American Immunodeficiency Group, CVID: Common variable immunodeficiency, Ig: Immunoglobulin, WBC: White blood cell

did not meet the CVID diagnostic criteria were analyzed according to age (0-5, 5-10, 10-16 and >16) (Table 8). Non-switched, switched memory B-cell s and serum, IgG, IgA, and IgM levels were lower in the age group of 0-5 years than those of the other group. The number of lymphocytes, the number of $CD4^+$ and $CD8^+$ cells, serum IgG, IgA levels of patients aged 5-10 years were lower compared to those of the same age group that did not meet the criteria. In patients older than 16 years, white blood cells (WBC) counts, IgG, IgA, IgM, the number of $CD4^+$ cells, levels unswitched B-cells were lower than those of who did not meet the criteria, but p values could not be calculated due to insufficient number of patients.

Although an autoantibody (ANA/antithyroid) positivity was found in 21 (62%) patients, it was negative in 13 (38%) patients. Comorbidity was found to be significantly more frequent in patients who had autoantibody (p=0.04).

Regular (400 mg/kg/month) intravenous or subcutaneous polyvalent immunoglobulin treatment was initiated in 16 patients (47%) who met the CVID criteria at the time of admission. The other 8 (23.5%) patients were given regular IVIG treatment because of the development of recurrent infections and/or comorbidities. Among the 24 patients who received IVIG treatment, 13 (54%) were children and 11 (46%) were adults. Ten (29.4%) patients were followed up without treatment.

Chemotherapy was initiated in two patients due to the development of malignancy (Hodgkin and Non-Hodgkin Lymphoma). No mortality was recorded in the patients.

Table 7. Immunological values of CVID patients who meet the ESID/PAGID criteria

P	Age	Mutation	Gender	Ig G (g/L)	Ig A (g/L)	Ig M (g/L)	Lymphocyte (10^3/µ/L)	$CD3^+$ cells	$CD4^+$ cells	$CD8^+$ cells	Switched B-cells	Unswitched B-cells	Naive B-cells
I	18 m	C104R	F	4.6 (6.7-8.5)	0.18 (0.3-0.5)	0.5 (1-1.3)	5.9 (4-10.5)	61 (51-80)	44 (27-55)	16 (12-30)	4 (2-16)	6 (1.6-16)	85 (68-96)
II	30 m	C104R	F	6.7 (7.1-9)	0.3 (0.5-0.7)	1 (0.9-1.2)	3.9 (2-8)	64 (57-81)	30 (23-52)	34 (12-35)	4 (2.9-31)	6 (4.8-20)	86 (46-85)
III	12 m	C172Y	M	3.7 (5-6.3)	0.06 (0.2-0.4)	0.2 (0.6-0.9)	5 (4-10.5)	70 (53-80)	48 (30-55)	21 (11-33)	0 (1.4-14.5)	2 (3.2-14.4)	91 (72-93)
IV	3 m	C193R	F	1.7 (5-6.3)	0.06 (0.2-0.4)	0.3 (0.6-0.9)	4.1 (2.5-16.5)	70 (53-80)	45 (30-55)	23 (11-33)	0 (1.4-14.5)	0 (3.2-14.4)	96 (72-93)
V	3	c.61+1G>A	M	4.9 (7.7-9)	0.4 (0.5-0.8)	0.5 (1-1.3)	4.5 (2-8)	56 (57-81)	40 (23-52)	14 (12-35)	4 (2-31)	10 (4.8-20)	68 (58-86)
VI	2 m	R6Q	F	2.7 (9-11)	0.1 (0.8-1.1)	1 (1-1.3)	6.9 (2.5-16.5)	72 (55-86)	42 (23-49)	30 (17-46)	7 (6.7-31)	5 (3.6-24)	70 (45-84)
VII	8	C104R	M	5.5 (9.1-1.1)	0.6 (0.8-1.2)	0.6 (0.9-1.3)	2.5 (1.5-7)	77 (55-86)	26 (23-49)	40 (17-46)	23 (6.7-31)	17 (3.6-24)	52 (45-84)
VII	6	C104R	M	4.5 (9.1-11)	0.5 (0.8-1.2)	0.5 (1-1.3)	2.2 (1.5-7)	52 (55-86)	26 (23-49)	22 (17-46)	5 (6.7-31)	13 (3.6-24)	77 (45-84)
IX	9	E140K	M	8.6 (9.3-1.1)	0.8 (0.9-1.1)	1.1 (9.6-1.3)	1.9 (1.5-6.8)	68 (58-86)	40 (27-47)	27 (17-39)	16 (2.7-29)	9 (2.4-22)	71 (44-88)
X	39	C104R	F	8.5 (11-14.5)	1.2 (1.6-2.3)	0.6 (1.1-1.6)	1.7 (1-4.8)	61 (64-85)	41 (32-57)	20 (14-39)	5 (6-34.5)	6 (5.3-32)	85 (34-79)
XI	34	C104R	F	4 (11-14.5)	0.2 (1.6-2.3)	3.8 (1.1-1.6)	0.8 (1-4.8)	64 (64-85)	32 (32-57)	30 (14-39)	3 (6-34.5)	66 (5.3-32)	24 (34-79)
XII	49	C104R	F	2.8 (11-14.5)	0.26 (1.6-2.3)	0.5 (1.1-1.6)	1.2 (1-4.8)	75 (64-85)	34 (32-57)	41 (14-39)	0 (6-34.5)	0 (5.3-32)	0 (34-79)
XII	39	C104R	M	5.3 (11-14.5)	0.78 (1.6-2.3)	0.3 (1.1-1.6)	1.2 (1-4.8)	66 (64-85)	44 (32-57)	21 (14-39)	25 (6-34.5)	46 (5.3-32)	25 (34-79)
XIV	25	C104R	M	1.7 (11-14.5)	0.06 (1.6-2.3)	0.04 (1.1-1.6)	2.2 (1-4.8)	67 (64-85)	45 (32-57)	32 (14-39)	4 (6-34.5)	27 (5.3-32)	67 (34-79)
XV	35	c.61+1G>A	M	5.4 (11-14.5)	0.8 (1.6-2.3)	0.3 (1.1-1.6)	2.9 (1-4.8)	47 (64-85)	29 (32-57)	18 (14-39)	20 (6-34.5)	45 (5.3-32)	26 (34-79)
XVI	19	C104R	M	6.8 (11-14.5)	0.38 (1.6-2.3)	2.8 (1.1-1.6)	1.8 (1-4.8)	67 (64-85)	35 (32-57)	32 (14-39)	15 (6-34.5)	25 (5.3-32)	53 (34-79)

ESID/PAGID: European Society of Immunodeficiencies/the Pan-American Immunodeficiency Group, CVID: Common variable immunodeficiency, P: Patient

Table 8. Immunological analysis of patients who meet and do not meet ESID/PAGID diagnostic criteria for CVID

	Meet ESID/PAGID diagnostic criteria for CVID				Do not meet ESID/PAGID diagnostic criteria for CVID			
	0-5	5-10	10-16	>16	0-5	5-10	10-16	>16
WBC (mm^3)	8670 ± 2500	6780 ± 1980	-	7035 ± 1190	6840 ± 2080	5380 ± 2850	8700 ± 2860	8370 ± 2210
Lymphocyte (mcL)	5096 ± 1164	2253 ± 305	-	1730 ± 730	4600 ± 728	2480 ± 1070	2320 ± 1480	2353 ± 640
Ig G (mg/dL)	408 ± 175	625 ± 214	-	498 ± 292	844 ± 132	862 ± 0	1420 ± 269	1350 ± 274
Ig A (mg/dL)	18.7 ± 14	70.9 ± 13	-	54.0 ± 42.0	59.6 ± 20	116.0 ± 0	92.6 ± 76.0	252.0 ± 231.0
Ig M (mg/dL)	104.5 ± 3.5	110 ± 2	-	232 ± 181	210 ± 144	107.0 ± 0	123 ± 140	300 ± 352
Navive B-cells	82.6 ± 11.3	66.6 ± 13	-	40 ± 29.4	60.0 ± 1.5	34.0 ± 48.0	68.0 ± 22.8	58.5 ± 16
Unswitched B-cells	4.8 ± 3.4	13.0 ± 4.0	-	30.7 ± 23.3	10.3 ± 2.8	9.0 ± 0	13.4 ± 14.3	16 ± 12.7
Switched B-cells (%)	3.1 ± 2.7	14.6 ± 9.0	-	10.2 ± 9.6	17.3 ± 0.5	2.5 ± 3.5	6.0 ± 5.4	9.7 ± 10.0
$CD4^+$ cells (%)	41.5 ± 6.2	30.6 ± 8.0	-	37.1 ± 6.2	31.3 ± 5.5	35 ± 15.5	38.6 ± 3.8	38 ± 4.2
$CD8^+$ cells (%)	23 ± 7.8	29.6 ± 9.2	-	27.7 ± 8.3	23.6 ± 6.5	35 ± 1.4	31.2 ± 6.5	25.4 ± 7.4
n	6	3	0	7	3	2	6	7

ESID/PAGID: European Society of Immunodeficiencies/the Pan-American Immunodeficiency Group, CVID: Common variable immunodeficiency, Ig: Immunoglobulin, WBC: White blood cell

Discussion

Generally, PID is not suspected or considered because the initial symptoms are missed in adults (17). Symptoms were detected in childhood in 27 patients (79.4%), but it was diagnosed in childhood in 18 patients. The initial signs of CVID are recurrent respiratory infections for most patients. Unfortunately, serum immunoglobulin levels cannot be routinely measured in such cases. Recurrent pneumonia, bronchiectasis, autoimmune and lymphoproliferative diseases of unknown origin suggest immunodeficiency.

The estimated prevalence of CVID in Turkey is 1.39/100.00 (18). It has been mentioned in many studies conducted in our country that the age of onset of symptoms varies between 3 and 7 years, and the age at diagnosis varies between 5.5 and 12 years (19,20). In different studies, the age at diagnosis showed 2 peaks in young adulthood between the ages of 6-10 and 26-40 years (21). The mean age of the pediatric patients who were diagnosed under the age of 18 years was 6.5 ± 5.18 years, and the mean age of the patients over the age of 18 years was 44.3 ± 14 years. As seen, although the ages varied in different countries and different studies, the age at diagnosis was consistent with the published data.

Both genders are equally affected by the disease (22,23). Twenty of the patients in the present study were male and 14 were female. Male gender was dominant in the study that was published by Erdem et al. (20). No significant differences were detected between male and female patients in terms of age of onset, age at diagnosis, immunoglobulin level, or leukocyte count (24). The fact that the number of male patients was higher in our patient group and that the age of symptom onset and diagnosis in girls was earlier than in boys (9.6 ± 11.8 girls, 11.1 ± 14.6 boys) suggests that this may be because of the low number of patients.

Familial events were reported in 5-25% of the cases (25). In the study that was conducted by Llobet et al. (26), this rate was reported as 32% and Karakoc-Aydiner et al. (19) reported that the rate of consanguinity was 75% in 20 CVID cases. In short, the rate of consanguinity differs according to geographical regions. The rate of consanguineous marriage was 23.5% and the rate of a positive family history was 55.8% in the present study.

It has been reported that the most common complaint in patients who have diffuse immunodeficiency is respiratory tract infections (25). The initial complaint of 23 (67.6%) patients was respiratory tract diseases in the study. Bronchial asthma was diagnosed in 4 (11.7%) patients and recurrent urticarial attacks in 3 (8.8%). Yong et al. (27) detected asthma in 29% of their cases. 11.7% of patients had asthma and 8.8% had recurrent urticaria attacks. The high prevalence of allergy and allergy-like symptoms in patients can be considered a result of the impaired balance of the cellular and humoral immune systems.

A total of 12 (35.2%) patients presented with abdominal pain, 5 (14.7%) patients had chronic diarrhea, and gastrointestinal complications were very common in CVID. A gastrointestinal disease was diagnosed in patients with CVID included Crohn's disease, ulcerative colitis, parasitic bacterial or viral infections, Celiac disease and intestinal lymphangiectasia (28). Celiac disease was disclosed in 1 patient and Crohn's disease was detected in 1 patient. However, follow-up processes of the patients suggest that this number may change.

It has been proven that C104R, A181E, C76R and R202H mutations cause the disease (29). A heterozygous pattern was detected in most patients (11). The fact that 47% of patients had C104R mutation and the heterozygous pattern was consistent with the literature data.

The mutation rate associated with TACI defects in IgA deficiency cases ranged from 0% to 16% (30). Most IgAD patients were asymptomatic and only one-third showed recurrent infections and/or autoimmunity (31). Four (11.7%) patients had selective IgA deficiency and 1 patient had partial IgA2 deficiency. Although autoantibody positivity was detected in all of these patients, no complaints or complications were notified, and they were followed up without treatment.

The number of B-cells was highly variable in patients having CVID (32) (12% had no detectable B-cells and 12% had decreased B-cells), 54% were within the normal range for B-cells (6-16% of circulating lymphocytes), 19% had slightly increased rates of B-cells (17-24%) and 5% had significantly increased rates. This reflects the range of potential B-cell defects that may be involved. Salzer et al. (33) noted that roughly 40-50% of CVID patients exhibit a total reduction in peripheral B-cells, while approximately 10% of CVID patients show significantly reduced or absent values specifically for B-cells. Disease progression tends to be more rapid and severe in such patients. The switched ($CD19^+IgD^-CD27^+$) B-cells, $CD3^+$, $CD8^+$ cells, WBC count and IgM levels values were found to be lower than those in patients who did not meet the CVID criteria. Statistical significance was detected only in IgA (p=0.02), IgG (p=0.0004) levels and lymphocyte counts (p=0.05). When the immunological parameters values of patients who met and did not meet the CVID diagnostic criteria were evaluated according to age (0-5, 5-10, 10-16 and >16), it was thought that the high WBC and lymphocyte counts might be secondary to infections. In our study, switched and non-switched B-cells of patients aged 0-5 years, $CD4^+$ cells and CD8 counts of patients aged 5-10 years, and non-switched B-cells and CD4 counts of patients over 16 years of age were low. Immunoglobulin levels were found to be low in all age groups.

Autoimmune complications, which are difficult to diagnose and clinically manage, are detected in approximately 20% of patients who have CVID (34). Age at diagnosis of autoimmunity is highly variable and may present before or after the diagnosis of immunodeficiency (35). In terms of prevalence, the most common autoimmune findings in CVID are ITP, cytopenia, hemolytic anemia, or autoimmune neutropenia, which is more rarely detected (32). A total of 21 of our patients had autoantibody positivity, 2 patients presented with the diagnosis of neutropenia and type 1 diabetes/celiac, and 8 (23.5%) showed autoimmune complications with a mean age of 25.1 ± 15.7 years. The most common C104 R mutation was found in the present study as; the most common autoimmune complication was thrombocytopenia. The prevalence of autoimmunity was higher in patients who had C104 R mutation (36). This was consistent with the published data. Therefore, it is recommended to carefully follow up the symptoms of TACI patients regularly for autoimmunity.

Splenectomy is recommended for patients who have CVID, when required (37). Specific morbidity associated with splenectomy was not reported in previous studies (38). Splenomegaly was observed in 4 of our patients, however, splenectomy was not indicated in these patients.

Bronchiectasis is an important and common medical problem causing serious respiratory problems and was identified in 4-76% of CVID patients (32,39). Bronchiectasis was diagnosed in 5.8% of the patients who have been followed at our clinic. Pulmonary infections of immunoglobulin replacement treatment and prophylactic antibiotics are today proven to be effective in prevention (40). Erdem et al. (20) reported lower IgA levels in patients who had bronchiectasis when compared to the patients who had other pulmonary complications. IgA level was below 7 mg/dL in one of the 2 patients presenting with bronchiectasis and within the normal range in the another. It was considered that this might be due of the low number of patients in our study.

The incidence of lymphoma increases in patients who have CVID. The incidence of lymphoma has been determined to be approximately 2-8%, and the most common malignancies are Non-Hodgkin Lymphoma and gastric cancers (23,27). Hodgkin Lymphoma is rare and was reported sporadically (20). A malignancy was diagnosed in 2 patients (5.8%), Hodgkin lymphoma was disclosed in 1 patient and Non-Hodgkin lymphoma in 1 patient. This was consistent with the literature data.

Granulomas are most frequently detected in the gastrointestinal system and lungs, with reported occurrences in the skin, spleen, and liver documented in the literature. The incidence of these non-caseification granulomas, especially resembling sarcoidosis, was reported to be 8-22% (41,42). ECC data from a multicenter European study showed that a severe decrease in the number of class-switched memory B-cells in 303 patients who had CVID was associated with granulomatous disease, splenomegaly and autoimmune cytopenia (43). One patient had diffuse nodules in the lungs and lymphocyte accumulation was detected in the biopsy, which was evaluated as lymphoproliferation in the present study. This was well below the rates that were published previously (27). This might be due to early diagnosis of the disease, patients receiving regular IVIG treatment and controlling infections.

The standard treatment for CVID is intravenous or subcutaneous immunoglobulin (400-600 mg/kg) replacement treatment (4). No evidence is available showing that this treatment protects against the development of malignancies, autoimmune diseases or granulomatous diseases, but it is considered to protect against bacterial infections (24,25). In a study conducted 50 patients, the number of patients who had pneumonia decreased from 84% to 22% after immunoglobulin treatment (44). Intravenous or subcutaneous polyvalent immunoglobulin treatment was administered for 24 patients were followed up in our study. As a results of vaccinations, the frequency of admission was reduced by 25% in 5 patients who presented with recurrent pneumonia. Two earlier studies reported mortality rates ranging from 19.6% to 6% in CVID patients (45,46). However, no mortality was observed in the patients included in our study.

Conclusion

The results of our retrospective study, encompassing 34 patients from a single center, align with TACI mutations reported in the literature. Nonetheless, our findings emphasize the importance of early immunological assessment and the prompt initiation of regular IVIG treatment to mitigate recurrent infections, comorbidities, and enhance the overall quality of life for patients.

Ethics

Ethics Committee Approval: The approval of the Ondokuz Mayıs University Faculty of Medicine Children's Hospital Ethics Committee was obtained for the study (approval no: 2022/447 date: 16.05.2023).

Informed Consent: Participating patients and their relatives were informed and consent forms were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.C., Concept: E.C., Design: E.C., E.A., S.I.K.K., A.Y., Data Collection or Processing: E.C., A.Y., Analysis or Interpretation: E.C., E.A., A.Y., Literature Search: E.C., A.Y., Writing: E.C., E.A.

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