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Five Years of Experience in a Single Center: Retrospective Analysis of Adult Patients with Common Variable Immunodeficiency

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ABSTRACT

Objective: Common Variable Immune Deficiency (CVID) is a heterogeneous immune disorder characterized by impaired and/or inadequate B cell differentiation with hypogammaglobulinemia. It is characterized by frequent and recurrent respiratory infections, autoimmune disorders, chronic lung diseases, granulomatous diseases, and increased risk for lymphoid malignancies.

Materials and Methods: The medical records of 47 patients (22 females, 25 males) who had been followed up at our clinic and had sufficient data in their files were retrospectively reviewed. Patients were diagnosed with CVID according to the ESID (European Society for Immunodeficiency) criteria.

Results: The median age of the patients was 32 (19-65) years. The most frequent clinical presentation of the patients was with recurrent upper respiratory infections (46%), pneumonia (29.8%), otitis media (23.4%) and chronic sinusitis (17%). During the follow-up period, 17 patients (36.8%) developed autoimmune complications, 14 (29.8%) of whom had autoimmune cytopenia. A total of 26 patients (55.3%) had bronchiectasis confirmed with computed tomography of the thorax. Lymphopenia was detected in 13 patients (27.7%). The median immunoglobulin level at the time of diagnosis was IgG 2.77 (0.33-6.90) g/L, IgM 0.31 (0.06-5.99) g/L, and IgA 0.25 (0.01-5.02) g/L.

Conclusion: CVID is very heterogeneous in terms of both clinical and laboratory features. Moreover, it is more common than expected, particularly in adulthood. The centers dealing with CVID should share their experiences in order to increase awareness among physicians.

Keywords: Bronchiectasis, common variable immune deficiency, hypogammaglobulinemia, IgG

INTRODUCTION

Common Variable Immune Deficiency (CVID) is a heterogeneous immune disorder characterized by impaired and/or inadequate B cell differentiation with hypogammaglobulinemia. It is characterized by frequent and recurrent respiratory infections, autoimmune disorders, chronic lung diseases, granulomatous diseases, and an increased risk for lymphoid malignancies (1-5). Although there are racial and geographical differences, CVID is estimated to affect 1 out of 25,000 people and is the most common symptomatic antibody disorder (1). Although more than half a century has passed since its identification, the pathophysiology is still unclear (6). An underlying genetic cause could be demonstrated in only 10% of the patients (7). A delay in diagnosis is frequent, especially in adult patients, due to the heterogeneity of the disease, its ability to affect many organs and systems, the decreased awareness of the physicians on this subject, and the perception that the immunodeficiency is a disease of childhood (7, 8). For this reason, sharing of CVID-related analyzes and experiences of the centers interested in primary immunodeficiency and collecting these data are very valuable, both for the recognition of the disease and for the management of the treatment before the

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development of disease-related complications (9, 10). Therefore, we aimed to present the demographic, clinical and biochemical features of 47 patients with CVID who were followed up at our immunology clinic.

MATERIALS and METHODS

Patients

The records of 47 patients (22 females, 25 males) who had been clinically followed up at our clinic and had sufficient data in their files were retrospectively reviewed. Patients were diagnosed with CVID according to the ESID (European Society for Immunodeficiency) criteria (11). The study protocol was approved by the Ethics committee. Informed consent was obtained from study participants.

Immunological Analyses

The quantitative evaluation of serum immunoglobulins (IgG, IgM, IgA and IgE) was performed by particle-enhanced immunonephelometry using the Siemens BN II / BN ProSpec system (Erlangen, Germany). Complete blood counts were performed with Sheath reagent using the Abbott Cell Dyn 3700 series (USA). Peripheral blood lymphocyte subsets were measured using the BD FACSCanto II flow cytometer with an eight-color configuration (San Jose, CA, USA) with fluorescent-labeled antibodies. Spirometric measurements were obtained using a common protocol with the nSpire ZAN 100 spirometer (Health Inc., Germany). At least three maneuvers were performed. However, additional maneuvers were also performed if one or more of the curves was unacceptable. The forced expiratory volume within one second (FEV1), FEV1 / FVC ratio (forced vital capacity), peak expiratory flow (PEF) and mean expiratory flow were recorded as 25-75% (MMEF25-75).

Statistical Analysis

Statistical analysis was performed with the IBM SPSS Statistics Version 22 software package. Normally distributed parameters were presented as mean ± standard deviation and skewed parameters were expressed as median (interquartile range [minimum/maximum]). Descriptive data were presented as frequencies and percentages and compared using the Chi-square test. Baseline characteristics were compared using the independent Student's t-test, Mann–Whitney rank-sum test, Fisher's exact test or Chi-squared test where appropriate.

Normal Values

With complete blood counts, the reference ranges in laboratory evaluations of the patients were 4 x 10^3/μL – 10 x 10^3/μL for white blood cells (WBC), 1.5 x 10^3/μL – 7.3 x 10^3/μL for neutrophils, and 0.8 x 10^3/μL – 5.5 x 10^3/μL for lymphocytes (12, 13).

Normal ranges for immunoglobulins were 5 g/L – 16 g/L for IgG, 0.4 g/L – 2.3 g/L for IgM, 0.7 g/L – 4 g/L for IgA and 5 IU/mL – 150 IU/mL for IgE (14, 15).

A tetanus IgG antibody level of ≥ 0.04 IU/mL and pneumococcal antibody level of ≥ 1.0 IU/mL were considered sufficient (16, 17). For isohemagglutinin titers, ≥1/16 was sufficient for anti-A while ≥1/8 was considered sufficient for anti-B (17).

In the evaluation of peripheral blood lymphocyte (PBL) subsets by flow cytometry, CD16-CD56 values of 5 – 31.3% for males and 3.5 – 24.9% for females; CD19 values between 6.3 – 20.8%; CD3 values of 48 – 82.6% for males and 56.8 – 84.1% for females; CD4 values of 23 – 52.6% for males and 26.9 – 55.5% for females; CD8 values of 12.8 – 40.2%; and a CD4/CD8 ratio of 0.68 – 3.61 were considered normal (18).

RESULTS

A total of 47 patients (female: 22 [46.8%], male: 25 [53.2%]) who were diagnosed or referred to our clinic with a diagnosis of CVID between 2013 and 2018 were retrospectively analyzed. The median age of the patients was 32 (19-65) years. The mean age at diagnosis was 28.2 ± 13.8 years (27.7 ± 14.8 years for males and 28.7 ± 12.9 years for females). The delay in diagnosis was 100.94 ± 92.52 months (99.9 ± 19.6 months for females and 101.8 ± 95.4 months for males). There was no statistically significant difference between genders in terms of both age at diagnosis and delay in diagnosis (p: 0.814, p: 0.944, respectively). One patient was diagnosed with a screening program performed since a person was diagnosed with CVID in the family, and 21 (44.7%) patients had parental consanguinity. The clinical and demographic characteristics of the patients are summarized in Table I.

The most frequent referral diseases of the patients were recurrent upper respiratory infections (46%), pneumonia (29.8%), otitis media (23.4%), and chronic sinusitis (17%). A total of four patients (8.5%) presented

to the clinic with autoimmune complications: three (6.4%) with autoimmune cytopenias and one patient (2.1%) with autoimmune hepatitis. During the follow-up period, 17 patients (36.8%) developed autoimmune complications, 14 (29.8%) of whom had autoimmune cytopenia. Six patients (12.8%) presented with symptoms of recurrent diarrhea and related malabsorption. Four patients were diagnosed with CVID following an etiological evaluation due to one patient having recurrent mastitis, one having orchitis, one having pneumococcal meningitis and one having sepsis. During the follow-up period, three patients developed malignant neoplasm (diffuse large B-cell lymphoma, MALT (mucosa-associated lymphoid tissue) lymphoma, splenic marginal zone lymphoma). Splenomegaly, another complication of CVID, was detected in 25 patients (53.2%) (Table II).

Twenty-six patients (55.3%) had bronchiectasis confirmed with a CT scan. There was no statistically significant difference between patients with bronchiectasis and patients without bronchiectasis in terms of a delay in diagnosis (p: 0.976). In seven patients, the pulmonary function tests could not be assessed due to the patient's inability to perform an acceptable test. Spirometry was normal in 14 out of 40 patients (35%). Twenty-five (62.5%) patients had airflow obstruction (FEV1 was below 80%) and MMEF was low in 33 (82.5%). Two patients had a history of lobectomy for bronchiectasis. One patient was diagnosed with GLILD (granulomatous-lymphocytic interstitial lung disease) with lung biopsy (Table III).

Four patients were diagnosed with CVID at another center and were receiving intravenous immunoglobulin (IVIG) infusion at regular intervals. Immunoglobulin replacement therapy was initiated in all patients after the diagnosis. Thirty-three patients (70.2%) received IVIG and 14 patients (29.8%) subcutaneous immunoglobulin (SCIG) replacement treatment. The median immuno-

Table I: Clinical, Demographic and Laboratory Characteristics of CVID Patients.

Characteristics (mean ± SD)	
Gender (Female), n %	22 (46.8%)
Age at diagnosis, years	28.2 ± 13.8
Age at diagnosis, male	27.7 ± 14.8
Age at diagnosis, female	28.7 ± 12.9
Current age, years	32 (19-65)
Diagnostic delay, months	100.9 ± 92.5
Diagnostic delay, months, male	101.8 ± 95.4
Diagnostic delay, months, female	99.9 ± 19.6
Parental consanguinity, n (%)	21 (44.7%)
IVIG, n (%)	33 (70.2%)
Antibiotic prophylaxis, n (%)	37 (78.7%)
Splenomegaly, n (%)	25 (53.8%)

IVIG: Intravenous immunoglobulin

Table II: Clinical Presentations of the Patients.

	Affected patients n (%)
Recurrent upper airway infections	20 (42.6)
Pneumonia	14 (29.8)
Otitis	11 (23.4)
Chronic Sinusitis	8 (17.0)
Recurrent skin lesions	6 (12.8)
Chronic Diarrhea	6 (12.8)
Autoimmune cytopenias	3 (6.4)
Mastitis	1 (2.1)
Autoimmune hepatitis	1 (2.1)
Family History of CVID	1 (2.1)
Meningitis	1 (2.1)
Sepsis	1 (2.1)

CVID: Common variable immune deficiency

Table III: Spirometry Results of the CVID Patients.

	FEV1	FVC	PEF	MMEF 25-75
>80% predicted, n (%)	15 (37.5)	18 (45)	5 (12.5)	7 (17.5)
60-79% predicted, n (%)	16 (40)	15 (37.5)	17 (42.5)	13 (33.5)
40-59% predicted, n (%)	7 (17.5)	6 (15)	12 (30)	12 (30)
<40% predicted, n (%)	2 (5)	1 (2.5)	6 (15)	8 (20)

FEV1: Forced Expiratory Volume in 1 second, **FVC:** Forced Vital Capacity, **PEF:** Peak Expiratory Volume, **MMEF 25-75:** Maximum mid expiratory flow between 25% and 75% of the FVC

globulin replacement therapy dose was 400 mg/kg/per 3 weeks (200-800 mg/kg/3 weeks). When patients receiving intravenous and subcutaneous immunoglobulin were evaluated separately, the median dose was 400 mg/kg/3 weeks (min: 200, max: 800 mg/kg/3 weeks) for IVIG and 133 mg/kg/week (83.3-266.3 mg/kg/week) for SCIG. During the follow-up period, azithromycin 500 mg/week was initiated in 35 patients (74.5%) and trimethoprim/sulfamethoxazole 800/160 mg/qod prophylaxis was initiated in two patients (4.3%).

Lymphopenia was present in 13 patients (27.7%). The median immunoglobulin level at the time of diagnosis was IgG 2.77 (0.33-6.90) g/L, IgM 0.31 (0.06-5.99) g/L, and IgA 0.25 (0.01-5.02) g/L. All patients had low IgG levels. The IgM level was high in one patient. The $CD3^+$ T-cell level in 2 patients (4.3%), $CD3^+CD4^+$ T cells in 11 patients (23.4%), $CD3^-CD16^+CD56^+$ natural killer cells in 13 patients (27.7%), and $CD19^+$ B-cells in 22 patients (46.8%) were lower than the reference ranges. Total $CD19^+$ B-cells of 10 patients (21.3%) was less than 1%. The $IgM^+IgD^+CD27^-$ naive B-cell rate was 83.1% (0-98.6), $IgM^-IgD^-CD27^+$ switched memory B-cell rate was 1.3% (0-52), and $CD4^+CD31^+CD45RA^+$ recent thymic emigrant (RTE) cell rate was 16.5% (0.9-69). There was no difference between the genders in terms of the RTE cell rate (p: 0.069). The $IgM^-IgD^-CD27^+$ switched memory B-cell rate was less than 2% in 25 patients (53.2%) (Table IV).

The isohemagglutinin titers could not be evaluated in three (6.4%) patients as their blood group was AB. The isohemagglutinin titers were sufficient in 17 patients (36.2%) and the titers were below the accepted reference range in 27 (57.5%). The anti-tetanus antibody response was insufficient in 9 patients (19.2%) and all of them produced sufficient antibody responses after receiving a booster injection. Anti-pneumococcal antibody titers could not be studied in three patients (6.4%) due to technical reasons. Anti-pneumococcal antibody responses were insufficient in 12 patients (25.5%).

DISCUSSION

Since CVID is a relatively rare disease and there is a lack of awareness about the disease, it is extremely important for the centers dealing with this patient group to share their knowledge and clinical experience about the disease, both to understand the pathophysiology of the disease and to reduce/prevent mortality and morbidity (10). Early diagnosis and early immunoglobulin treatment of this umbrella disease, which can have very different clinical presentations, will protect patients from serious morbidity and mortality.

Table IV: Immunological Parameters of the CVID Patients.

	n	Mean/median values	Reference ranges
Neutrophil, (cell/ ul)	47	4127± 2551	1.5 10^3/ul-7.3 10^3/ul
Lymphocyte, (cell/ ul)	47	1750 ± 1375	0.8 10^3/ul-5.5 10^3/ul
Platelet, (cell/ ul)	47	212160 ± 930173	150-400000 cell/ ul
IgG level at diagnosis	47	2.77 (0.33-6.90)	7-16 g/l
IgM level at diagnosis	47	0.31 (0.06-5.99)	0.4 - 2.3 g/l
IgA level at diagnosis	47	0.25 (0.01-5.02)	0.7 -4 g/l
CD3+ T cells (%)	47	76.8 ± 11.4	Male: 48-82.6 % Female: 56.8-84.1%
CD3+ CD4+ T cells (%)	47	32.4 ± 14.4	Male: 23-52.6 % Female: 26.9-55.5 %
CD3+ CD8+ T cells (%)	47	38 (19-74)	12.8-40.2 %
CD4/CD8	47	0.77 (0.1-3.58)	0.68-3.61
CD19+ B cells (%)	47	7.1 ± 5.7	6.3-20.8 %
CD3- CD16+ CD56+ NK cells (%)	47	7.2 (0-53)	Male: 5-31.3% Female: 3.5-24.9%
IgM+ IgD+ CD27- B cells (%)	46	83.1 (0-98.6)	
IgM- IgD- CD27+ B cells (%)	47	1.3 (0-52)	
CD4+ CD31+ CD45RA+ Recent Thymic Emigrant Cells (%)	44	16.5 (0.9-69)	

Ig: Immunoglobulin, **CD:** Cluster of differentiation

Oksenhendler et al. reported that 56.3% of the patients were female and 43.7% were male (7). In a study evaluating 2212 CVID patients, 51.1% of the patients were female and 48.9% were male (19). In studies performed in Turkey, Ardeniz et al. reported a female to male ratio of 1 to 1.3 while Muşabak et al. reported this ratio as 1 to 1.6 (10, 20). Our present study included 22 (46.8%) females and 25 (53.2%) males, which indicated a higher number of male patients similar to other studies performed in Turkey.

In a DEFI French national study of CVID, the median age at diagnosis was reported as 33.9 years. The median age of diagnosis was 36.6 years for females and 30.5 years for males, and a statistically significant difference was identified between the genders in terms of median age at diagnosis (7). Similarly, Thickett et al. reported the age at diagnosis to be higher in females (females: 46.9 years, males: 33 years) (21). Gathmann et al. showed that complaints in men began at an earlier age and that men were diagnosed earlier (19). In Turkey, Ardeniz et al. reported that the median age at diagnosis was 33 years (17-73) for women and 28 years (13-49) for men (20). In the present study, the mean age at diagnosis was 27.7 ± 14.8 years for males and 28.7 ± 12.9 years for females. We can conclude that these values are in line with the literature. In men, the earlier onset of complaints may be due to the fact that Btk analyses could not be performed in some X-linked patients (such as X-linked agammaglobulinemia) and these patients were therefore monitored and assessed as CVID. Furthermore, male sexual hormones accelerate thymic involution, which may cause men with immunodeficiency to be diagnosed earlier (22). In addition, Pido-Lopez et al. have shown that thymic output was increased in women compared to men (23). This may result in late diagnosis in the women.

In a study conducted in Turkey, Muşabak et al. reported the rate of parental consanguinity as 12.7% (10). In another study in Turkey, the rate of consanguinity was 30% (21). In a DEFI group study, parental consanguinity was determined in 11.6% of CVID patients (7). In the present study, this rate was higher (44.7%). The reason for this difference was probably the racial, socioeconomic and geographical differences.

Delayed diagnosis remains a major problem for CVID patients. Although the first complaints emerge during childhood in many patients, some patients cannot be diagnosed until adulthood. In a study by Oksenhendler et al., the delay in diagnosis was 6.9 years (0-55 years) (7). Another study reported the delay in diagnosis as 3 years for males and 7 years for females (21). In a study by the ESID Registry Working Party, the median delay in diagnosis was 4.1 years (19). The same study reported a shorter delay in diagnosis in male patients (3 years for males and 5 years for females). In a study conducted in Turkey, the delay in diagnosis was 15 (1-32) years in females and 8 (1-31) years in males (20). In our study, the delay in diagnosis was 100.94 ± 92.52 months (99.9 ± 19.6 months for females, 101.8 ± 95.4 months for males), which is consistent with the literature.

Many studies have shown that recurrent upper respiratory tract infections are the most common cause of admissions in CVID patients (2, 7, 20, 24, 25). Thickett et al. reported recurrent pulmonary infections and productive cough as the most common causes of admission (89.7% of patients) (21). In our current study, the most common reason for admission was respiratory tract infections such as pneumonia, chronic sinusitis and recurrent otitis media.

Autoimmune conditions require special attention in CVID patients. While autoimmune complications may be the reason for admission in 25% of the patients, these may develop after CVID diagnosis in some patients and without a CVID diagnosis in other patients (26). In addition, treatment modalities such as steroid therapy and splenectomy, which are used for the treatment of autoimmune presentations in patients, may aggravate underlying immunodeficiencies (27). In the DEFI study, the rate of patients with autoimmune conditions at first admission was 10%. In the same study, the rate of autoimmune cytopenia during follow-up was reported as 18% (7). In a study of 311 CVID patients, 37% of the patients had autoimmune complications and 17.6% had autoimmune cytopenia. In our current study, 8.5% of the patients presented with autoimmune complications while 36.8% had autoimmune complications and 28.8% had autoimmune cytopenia during the follow-up period. Our data is similar to literature data in terms of both hematologic cytopenias being the most common autoimmune complication and the rate of autoimmune complications.

Splenomegaly is common in CVID patients and may develop due to lymphoid hyperplasia and granulomatous disease, as well as concomitant liver diseases and portal hypertension. In the study by Oksenhendler et al., the rate of splenomegaly was 38% (7). In another study, there

was splenomegaly in 26% of the patients (25). Gathmann et al. reported that patients with splenomegaly had lower IgG levels than patients without splenomegaly (19). The highest incidence of splenomegaly in CVID patients was reported in Germany with 62% (19). In the current study, splenomegaly was detected in 25 patients (53.2%) and this rate is consistent with the literature.

The incidence of non-Hodgkin lymphoma increases significantly in CVID patients. Cunningham-Rundles et al. reported that the risk of lymphoma in female CVID patients was 478-fold higher than in a similar age group (28). In another study, the incidence of lymphoma was reported to be 6.3% in CVID patients (7). Therefore, it is necessary to inform patients about the increased risk of lymphoma and to closely monitor them for lymphoma signs such as weight loss, night sweats, fever and permanently enlarged lymph nodes. In a study by Ardeniz et al., lymphoma developed in three out of 23 patients during the follow-up (20). In our study, malignancy developed in three patients during the follow-up period and all of these malignancies were non-Hodgkin lymphoma.

Bronchiectasis may occur secondary to recurrent pyogenic lung infections with or without underlying immunodeficiency (29). Aghamohammadi et al. have reported a 47% incidence of bronchiectasis in CVID patients (29). Gathmann et al. have reported different incidence rates from different centers in a group of 2122 CVID patients, and reported that the incidence rate of bronchiectasis ranged from 6% to 66% in CVID patients (19). In the same study, Gathmann et al. have reported lower IgM levels and a longer delay in diagnosis in patients with bronchiectasis (19). In our study, CT-confirmed bronchiectasis was detected in 26 patients (55.3%), which was higher than observed at the CVID centers in the study by Gathmann et al. Karaca et al. suggested a lower incidence of lower respiratory tract infections in CVID patients with parental consanguinity (30). The relative higher frequency of consanguineous marriages in our study may have resulted in a higher incidence of bronchiectasis in our patients. In addition, Thickett et al. have shown that a low number of switched memory B cells was more frequently associated with bronchiectasis (21). In the current study, the low number of switched memory B cells in 25 patients (53.2%) may have increased the incidence of bronchiectasis.

Immunoglobulin replacement is the basis of CVID treatment. Different doses, different dose ranges and different trough levels are targeted between centers. Gathmann et al. reported the median immunoglobulin dose as 460 mg/kg/4 weeks (min: 129 mg/kg/4 weeks-750 mg/kg/4 weeks) (19). At our clinic, we aim to maintain the IgG level at 9 g/L and above by initiating IVIG at a dose of 400-600 mg/kg at 3-week intervals. We check trough IgG levels at 3-month intervals, but more frequently at the time of initial diagnosis. After reaching the IgG > 9 g/L target, we decide on the appropriate method of immunoglobulin replacement (IVIG or SCIG) with the patient.

Prophylactic antibiotics are often used to prevent the development of bronchiectasis and reduce the frequency of infections in CVID patients. Prophylaxis is recommended to prevent opportunistic infections such as Pneumocystis carinii (P. jirovecii), particularly in patients with a $CD4^+$ T lymphocyte count of <200 cells/ml. Muşabak et al. reported initiating prophylactic antibiotics in 13 out of 31 CVID patients (41.9%) (10). Ardeniz et al. initiated prophylactic antibiotics in five out of 23 patients (21.7%) (20). The rate of prophylactic antibiotic use was 74.5% in the current study. Prophylactic antibiotic therapy is initiated for every CVID patient with bronchiectasis at our center. As reported in previous studies, we often prefer macrolide antibiotics for prophylaxis due to their additional anti-inflammatory effects in CVID patients, since the development of bronchiectasis is not only associated with immunoglobulin levels but also reflects additional inflammatory processes (31). The high rate of prophylactic antibiotic use may be related to this fact.

Although the flow cytometric evaluation of leukocytes is not mandatory for the diagnosis of CVID, flow cytometry abnormalities are frequently observed in these patients. Decreased memory B-cell ($CD27^+$ B cells) counts and decreased switched memory B-cell ($CD27^+$ IgD^-IgM^-) counts in particular have been reported (32). Therefore, the EUROclass criteria has classified CVID patients according to B-cell lymphopenia, decreased switched memory B-cells, $CD21^+$ B-cells, and transitional B-cells (32). In a study investigating 252 CVID patients, the B cell rate was ≤ 1% in 13.5% of patients. In the same study, severely reduced switched memory B-cells were detected in 39.3% of the patients (IgD^-CD27^+ B cells ≤2%) (7). The rate of switched memory B-cells has been shown to be associated with clinical complications independent of the immunoglobulin level in CVID patients (24). In

addition, Piqueras et al. identified a high prevalence of splenomegaly, lymphoid proliferation and granulomatous disease in CVID patients without memory B-cells (33). In our study, the $CD19^+$ B-cell rate of 10 patients (21.3%) was less than 1%. The $IgM^-IgD^-CD27^+$ switched memory B-cell rate was less than 2% in 25 patients (53.2%).

It has been shown that T-cell migration from the thymus is decreased in CVID patients compared to healthy individuals and $CD31^+CD4^+$ T-cells (RTE Cells) have been demonstrated as the cells that migrate from the thymus (34). Unlike $CD31^-CD4^+$ T-cells, RTE cells do not proliferate at the periphery and are an indirect indicator of thymic capacity (34). Oraei et al. have shown that the RTE cell rate decreased in male CVID patients compared to both female CVID patients and healthy individuals (35). Bateman et al. also showed that the RTE cell rate decreased in CVID patients, which was more evident in CVID patients with polyclonal lymphoproliferation, autoimmune cytopenia, and organ-specific autoimmune disease (36). Although Oraei et al. and Pido-Lopez et al. showed that thymic output was increased in women compared to men, no difference was found between the sexes for RTE cells in the current study (23, 35).

In conclusion, CVID is very heterogeneous in terms of both clinical and laboratory features. Moreover, this disease is more common than expected, particularly in adulthood. This requires the follow-up of these patients with a multidisciplinary team study. Inadequate awareness of CVID delays the diagnosis, affects the quality of life, and increases morbidity and mortality in the patients. It is therefore very important for centers dealing with CVID to share their experiences.

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None

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

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