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Follow-up and treatment of patients with Common Variable Immune Deficiency: A single-center experience

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ABSTRACT

Objectives: Common Variable Immunodeficiency (CVID) is a primary immunodeficiency characterized by immunoglobulin production defect. Our study aimed to create awareness of primary immunodeficiency in adult patients, establish standard approaches for clinical follow-up of CVID patients, and reveal the clinical characteristics of CVID patients in our region.

Method: The study was conducted in patients with diagnosed and newly diagnosed CVID. The demographic and clinical characteristics of the patients and their treatment data were analyzed retrospectively and prospectively.

Results: Thirteen of our patients were female and 12 were male. The mean age at diagnosis of the patients was 30.32 (2-57) and the mean delay in diagnosis was 9.32 months (0-30). The most common clinical finding of our patients at the time of admission was an infection. Among the infections identified, 3 patients had URTI, 19 had LRTI, and 2 had gastroenteritis. In 16 of our patients, bronchiectasis was detected at the time of diagnosis, and in 1 during the follow-up period. In the examinations performed in terms of organomegaly, splenomegaly was found in 11 patients and hepatomegaly was found in 8 patients. When patients were screened for autoimmune disease, ITP and celiac were found in 2 patients at the beginning, while autoimmune thyroiditis was developed in 1 patient and SLE in 1 patient during follow-up. Our patients were given IVIG treatment at regular intervals. The number of reactions seen in a total of 421 IVIG infusions was two.

Conclusion: Primary immunodeficiencies should definitely be considered in patients with recurrent infections and resistance to antibiotic therapy. Patients should be followed according to established follow-up and treatment protocols in order to reduce and diagnose complications.

Keywords: CVID, primary immunodeficiency, follow-up and treatment protocols

Primary immunodeficiency is related to the defect in the development, function, or both of the immune system and may present as 200 different etiologies and clinical manifestations. Antibody-associated humoral primary immune system accounts for 65% of primary immunodeficiencies. Common variable immunodeficiency (CVID) is the most common of this group of diseases. CVID is a primary immunodeficiency disease characterized by defective production of immunoglobulins due to impaired B cell differentiation. [1]

The prevalence of the disease varies between 1:10,000 and 1:100,000 according to different populations, and both sexes are equally affected.

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Typically, the age of onset of symptoms is after puberty and before the age of thirty. However, it has been reported that it has an early peak between the ages of 1-5. Although the disease is usually sporadic, familial transmission has been reported at a rate of 20%.[4]

It is very difficult to diagnose because CVID patients present with different symptoms and complications. Therefore, the diagnosis can often be made years later. The average delay in diagnosis was found to be 7.46 years in the European study conducted in CVID patient groups, and 8.9 years in the Italian study.[5-6] In a study conducted with 23 adult patients in our country, it was found that there was a delay in diagnosis of 8 years in women and 15 years in men.[7] The main reason for the delay in diagnosis is the lack of awareness of primary immunodeficiency in adult patients.

The diagnosis is made based on the clinical and laboratory features of the disease. While clinical examination may be normal in CVID patients, growth retardation and weight loss may be seen due to chronic disease. Findings such as oral candidiasis, gingivitis, tooth decay, cobblestone view on the posterior pharyngeal wall supporting chronic sinusitis, chronic perforated or scarred tympanic membrane image, clubbing in the fingers due to chronic lung disease can also be detected in the physical examination. In addition, lymphadenopathy, splenomegaly, arthritis, and skin findings related to the autoimmune disease are seen in some CVID patients.[8] In patients with CVID, routine laboratory tests such as complete blood count and urinalysis are usually not impaired. On the other hand, a decrease in globulin and/or total protein levels and lymphopenia can be detected in laboratory tests. Serum immunoglobulin levels are below two standard values for age.[9]

Another important problem in CVID patients is the follow-up process after diagnosis. Since clinical immunology has not progressed as much as basic immunology in our country, it has not been clarified who does or should do the clinical follow-up of adult immunodeficiency patients. There are no standard follow-up protocols for CVID patients both in our country and in the world. It is not clear how, how often, and for which problems these patients should be checked. This study, firstly, it was aimed to contribute to the formation of a protocol that will determine the clinical follow-up principles of CVID patients who are not under regular follow-up, and secondly, to reveal the clinical characteristics of CVID patients present in the region.

METHODS

The study protocol was approved by the Medical Ethics Committee of Necmettin Erbakan University. Written informed consent was obtained from all subjects included in the study. Twenty-five patients with CVID (13 females, 12 males; mean age, 36,60 ± 13,49 years) followed up by the Immunology and Allergy Department were included in the study.

The diagnosis of CVID was made according to the following criteria,

-Presence of all of the following criteria in a male or female patient who has a significant decrease in IgG levels (at least 2 SD below the mean values for age) and at least one of the low IgM or IgA levels,

1) Onset of immunodeficiency after 2 years of age,

2) Absence of isohemagglutinins and/or weak immune response to vaccines,

3) Exclusion of other causes of hypogammaglobulinemia.

Creation of follow-up documents

Standard guidelines and file forms that could be used in follow-up were not available for this group of patients. For this reason, a file format was prepared specifically for the study, containing information such as patient identity information, history, family history, disease history, previous examinations, examinations to be performed during diagnosis and follow-up, follow-up and treatment features, follow-up of complications, and treatment results.

Data collection

All records of all patients previously diagnosed with CVID were reviewed retrospectively. Files and epicrisis records from different clinics were collected. Data were processed into a CVID tracking file.

In addition, data collection was continued prospectively in the study. For this purpose, patients residing in Konya were called for control visits every 3 weeks, and those residing in distant places at least every 3 months. It was aimed to complete all the missing tests in the control visits and diagnose new complications. The general condition of the patients and changes in their quality of life was questioned. These inquiries were carried out by contacting the patients who did not or could not attend the control by telephone.

Informing the patient

Patients were interviewed about CVID disease.

Information was given about the cause, course, treatment, and complications of the disease. Family screenings of existing patients were performed. First-degree relatives were evaluated first. The possibility of disease in more distant relatives was explained to the patients, and it was aimed at people with complaints to apply to our clinic. In addition, the parents of pediatric patients diagnosed with CVID in the Department of Pediatric Immunology Allergy were evaluated for CVID in our clinic.

Determination of treatment standards

Certain standards have been introduced for immunoglobulin replacement therapies, which are administered intravenously. Intravenous Immunoglobulin (IVIG) doses are individualized. Clinical nurses were trained in infusion techniques. A standard IVIG infusion "order" was prepared and treatments were performed accordingly. An informed consent form was prepared for IVIG infusions, which are the basis of treatment, and an IVIG consent form was obtained from all patients. In addition, the patients were evaluated in terms of the need for prophylactic antibiotics. Prophylactic antibiotic therapy was initiated in patients with chronic lung disease or a history of frequent and prolonged infections.

Statistical analyses

Clinical and experimental data were analyzed using Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics for each variable were determined. Data were expressed as mean ± standard deviation or median and frequency.

RESULTS

Demographic findings and general characteristics

Of the 25 patients who participated in the study, 11 of them were adult patients diagnosed with CVID and still being followed by the Pediatric Immunology and Allergy Department, and 6 of them were adult CVID patients diagnosed in the Meram Medical Faculty Hospital Immunology and Allergy Diseases Department outpatient clinic. The remaining 8 patients were adult patients who were diagnosed with CVID and were not followed up in a specific clinic and were only receiving regular or irregular IVIG therapy. The mean age of diagnosis was 30.32 ± 13.84 years (10-57 years). The mean delay in diagnosis was 107.04 ± 95.61 months (0-360 months). Our patients were investigated with a pedigree in terms of consanguineous marriage. While 2 of our patients were siblings, consanguineous marriage was detected in 9 (36%) of our patients.

Findings at the time of diagnosis

When the admission symptoms of the patients were evaluated, it was determined that 92% of them presented with infection, 4% with treatment-resistant skin lesions, and 4% with diffuse lymphadenopathy. Among the infections identified, 3 patients had upper respiratory tract infections, 19 had lower respiratory tract infections, and 2 had gastroenteritis. When all patients were evaluated, two patients had concomitant chronic sinusitis, one patient had congestive heart failure, one patient had coronary artery disease, two patients had heart valve replacement history, one patient had the rheumatic disease, one patient had epilepsy, and one patient had psoriasis. In addition, one of our patients was followed up with hereditary hemorrhagic telangiectasia. Apart from these, one of our patients was under dialysis treatment due to chronic renal failure due to amyloidosis.19 of our patients (76%) had a history of recurrent pneumonia and hospitalization due to pneumonia at the time of admission. There was bronchiectasis in 16 (64%) of 25 CVID patients followed up in our clinic. In addition, one of our patients had a history of pneumonectomy for bronchiectasis.

When all patients who were followed up for CVID and participated in our study were examined in terms of admission complaints, the number of patients who applied for gastrointestinal complaints was 3 (12%). One of our patients was previously diagnosed with celiac due to malabsorption. At the time of admission, giardiasis was detected in 5 patients. Only 2 of the patients with giardiasis in stool analysis had gastroenteritis. When our patients were questioned in terms of inflammatory bowel disease, ulcerative colitis was found in one of our patients. 25 CVID patients participating in the study were screened for hepatitis A, hepatitis B, and hepatitis C at the time of diagnosis. While A and C positivity was not detected in any of the patients, hepatitis B positivity was detected in 2 patients who were being followed up by gastroenterology. In another patient who had been followed up in another center before, HBV DNA was found to be positive despite HBs-Ag negativity.

Hepatosplenomegaly, which is one of the complications that can be seen in CVID patients, was

checked with ultrasonography (USG) at the time of diagnosis. Splenomegaly was found in 11 (44%) of our patients, and hepatomegaly was found in 8 (32%) patients. Six patients (50%) with splenomegaly also had hepatomegaly. One of our patients had a history of splenectomy due to immune thrombocytopenia (ITP). Our patients were examined for malignancy at the time of diagnosis. There was no finding suggestive of malignancy in any of the patients. These data are summarized in Table 1.

Findings during follow-up

Our patients who participated in our study were scanned with high-resolution computed tomography (HRCT) for bronchiectasis at regular intervals and according to their symptoms. Newly developed bronchiectasis was detected in a patient with dyspnea, cough, and sputum complaints. In addition, patients were screened for organomegaly at regular intervals during their follow-ups. While it was observed that splenomegaly developed in a patient who did not have

Table 1. Demographic and clinical features of patients

	Age	Gender	Complaint	Findings at the time of diagnosis	Findings during follow-up
1	20	Male	URTI	-	Bronchiectasis
2	47	Male	URTI	Bronchiectasis, ITP, splenectomy	Surgeryfor sinusitis
3	26	Male	Gastroenteritis	Bronchiectasis	Splenomegaly
4	35	Female	LRTI	Bronchiectasis	--
5	53	Female	LRTI	Hepatomegaly	-
6	59	Female	Gastroenteritis	Bronchiectasis, Splenomegaly, Hepatomegaly, Celiac Disease	-
7	22	Female	LRTI	Bronchiectasis, Hepatomegaly	Improvement in hepatomegaly
8	27	Female	LRTI	Bronchiectasis, Splenomegaly	Pregnancy
9	52	Female	LRTI	Splenomegaly	-
10	60	Male	LRTI	Coronary artery disease	Atopy
11	27	Male	Skin lesion	Bronchiectasis, Splenomegaly, Hepatomegaly, Psoriasis	-
12	30	Female	LRTI	Splenomegaly	-
13	32	Male	LRTI	Bronchiectasis	-
14	25	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly	Amyloidosis
15	21	Female	LRTI	Bronchiectasis	Thyroiditis
16	20	Female	URTI	-	SLE
17	30	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly, CKD	
18	30	Female	LRTI	Bronchiectasis	Pregnancy
19	61	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly	Cirrhosis
20	40	Male	LRTI	Splenomegaly	-
21	39	Female	LRTI	-	-
22	24	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly	-
23	45	Male	LRTI	Bronchiectasis, Splenomegaly, rheumatoid arthritis	-
24	37	Female	LRTI	Bronchiectasis, Atopy	-
25	53	Female	LRTI	Coronary artery disease, lymphadenopathy	-

organomegaly at the beginning, hepatomegaly was observed to regress in the abdominal USG performed in the follow-up of a patient who was found to have hepatomegaly at the time of diagnosis.

Patients were screened for autoimmunity at regular intervals during follow-ups. Autoimmune thyroiditis was detected in one patient other than our patients with celiac and ITP diagnoses mentioned above. In addition, systemic lupus erythematosus was detected in one of our patients during follow-up.

Patients were screened for malignancy at regular intervals during follow-up, and none of them found any malignancy. Liver cirrhosis was observed in one of our patients, who was followed up abroad during the winter months and followed up by us in the summer, who had hepatitis B positivity at the time of diagnosis and was receiving antiviral treatment. During the follow-up, one of the patients applied to us with a general condition disorder, shortness of breath, pleural effusion, and diffuse edema. The patient with hypoalbuminemia was found to have 11 g of proteinuria in the 24-hour urinalysis. The patient was consulted with the nephrology outpatient clinic and a renal biopsy was planned. The biopsy result was compatible with amyloidosis. Except for this patient, no proteinuria was detected in any of the patients. One patient with chronic renal failure was not included in the screening.

Two of our patients who were followed up in our clinic due to CVID became pregnant during their follow-up. Our patients who continued IVIG treatment delivered without complications. The findings detected during the follow-up are summarized in Table 1.

URTI Upper respiratory tract infection, LRTI Lower respiratory tract infection, ITP Immune thrombocytopenia, CKD Chronic kidney disease

Data on treatments

IVIG replacement (400-600 mg/kg) was applied to all of our patients. While 25 patients (96%) were treated with IVIG at 21-day intervals, intravenous immunoglobulin replacement was applied to our patient with nephrotic syndrome at 15-day intervals.

Reactions were observed in 2 patients during IVIG infusions. Infusions were continued by controlling the reactions depending on the infusion rate with appropriate approaches (Table 2). The number of reactions seen in 421 infusions made during the study was 2.

DISCUSSION

As in the whole world, there is positive progress in health in our country, and as a result, life expectancy in chronic diseases is prolonged. In the past, children with immunodeficiency could not reach adulthood, so adult doctors had limited knowledge about this issue. However, the increase in the quality of treatment and care now necessitates adult physicians to have knowledge about this issue. Our study aimed to raise awareness among physicians of adult immunodeficiency diseases and to provide data for protocols that will set the follow-up and treatment of diagnosed patients to certain standards.

Antibody-associated humoral primary immunodeficiencies constitute 65% of primary immunodeficiencies, and CVID is the most common of this group of diseases. CVID is a primary immunodeficiency disease characterized by defective production of immunoglobulins due to impaired B cell differentiation. One of the most important problems in this group of patients is the delay in diagnosis. In our study, the mean age of symptom onset was 21.24 ± 17.18 years, while the mean age at diagnosis was 30.32 ± 13.84 years. The mean delay in diagnosis was 107.04 ± 95.61 months. In the literature, an average of 7.46 years in the European study on CVID patient groups, and 8.9 years in the Italian study were shown to be delayed in diagnosis.[5-6] In a study conducted with 23 adult patients in our country, it was found that there was a delay in diagnosis of 8 years in women

Table 2. Intravenous Immunoglobulin therapy administration protocol

	With infusion pump	With serum set
First 10 minutes	10 ml/hour	4 drops/minute
Next 20 minutes	20 ml/hour	8 drops/minute
Next 20 minutes	50 ml/hour	18 drops/minute
Next 60 minutes	100 ml/hour	32 drops/minute
The remainder of the infusion (Maintenance)	200 ml/hour	64 drops/minute

and 15 years in men.[7]

CVID is usually seen as sporadic cases. Familial transmission has been reported at a rate of 20% in the literature. [10] However, consanguineous marriage increases the incidence of the disease. 9 of our patients had consanguineous marriage and 1 patient was diagnosed with CVID as a result of family screening.

Pulmonary function tests and direct radiographs are limited in the follow-up of patients in terms of pulmonary complications. Pulmonary function tests can be useful in the follow-up and treatment evaluation of patients with chronic lung disease, and they can be applied at the diagnosis stage and when the clinical situation requires it. High-resolution lung tomography is very valuable in the evaluation of patients for bronchiectasis. However, there is no consensus on how often it should be applied. It is recommended to be drawn every 3-5 years from different sources and literature. [11-12] In addition, CVID patients are radiosensitive, there is insufficient knowledge about 'safe dose radiation', and imaging is needed for other pulmonary complications other than bronchiectasis. There are reservations about the follow-ups to be made with imaging. In our center, we evaluated our patients with HRCT every two years in terms of pulmonary complications, and those with symptoms in a shorter time.

Screening of patients for gastrointestinal complications is important because of the chance of early detection and treatment. Ultrasonography, endoscopy, parasite examinations, and liver enzyme monitoring are recommended. Endoscopy is one of the methods used in screening because of the increase in gastric cancer compared to the normal population. While some researchers argue that endoscopy should be performed every 2 years, there are also researchers who argue that the frequency of follow-up should be determined according to the initial findings.[13-14] It is recommended that USG be done annually, and parasite examination should be done during the routine examination. Since antibody production is insufficient in the follow-up of infections such as hepatitis B and C, viral load should be checked. In terms of nodular regenerative hyperplasia, another gastrointestinal complication, patients should be followed up with liver enzymes, and biopsy is recommended, especially if the ALP level is above 1.5 times for more than 6 months. [15] In our center, we screened patients with liver function tests at 6-month intervals and with abdominal USG at 2-year intervals.

Hemogram is usually sufficient for follow-up for hematological complications. Although it is not known at what intervals it should be done, it is recommended to be done every 3-6 months. Newly emerging symptoms and physical examination findings are important in terms of autoimmune diseases and malignancy. Examining autoantibodies at the diagnosis stage may help to explain the unknowns among CVID autoimmune diseases. It is recommended that patients who do not have additional findings in terms of malignancy should be screened according to the methods and intervals determined in the healthy population.[16-17] In line with these data, we screened our patients for autoimmunity every 6 months and for malignancy once a year.

While CVID patients had high mortality and morbidity in the past, today their life expectancy has increased considerably with appropriate treatment and follow-up. The mainstay of treatment is immunoglobulin replacement therapy, antibiotic therapy for infections, and supportive therapy for non-infectious complications. [18] The goal of immunoglobulin replacement therapy is to bring Ig levels to the normal range or to a value where infections are reduced. Ig half-life is 3 weeks on average and stable levels can be reached after 3-6 months of treatment. Intravenous and subcutaneous administration of IVIG therapy has been found to be equally effective and safe.[19] Although these treatments have been applied for a long time, there are differences between the centers in terms of application forms due to the side effects observed during the application. We created our own application protocol in our center and gave IVIG treatment to patients every 21 days.

As a result; CVID patients are patients who need close and special follow-up from the moment of diagnosis. There is a need for standardized treatment and follow-up protocols, especially in adult patients, in order to recognize and perhaps prevent complications in the early period, to keep the quality of life high, and to prolong survival. We think that the data and experience obtained from this study will be a source for such protocols.

CONCLUSION

None of the authors have any relationships with or financial interests in companies related to the findings of this work. None of the authors declare any conflicts of interest.

Contribution

Study Conception: AZÇ, ZY,; Study Design: AZÇ, ZY,; Supervision: AZÇ, ZY,; Materials: AZÇ, ZY,; Data Collection and/or Processing: AZÇ, ZY,; Statistical Analysis and/or Data Interpretation: AZÇ, ZY,; Literature Review: AZÇ, ZY,; Manuscript Preparation: AZÇ, ZY and Critical Review: AZÇ, ZY.

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