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Common variable immunodeficiency in adults requires reserved protocols for long-term follow-up

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Background/aim: The aim of this study is to establish follow-up protocols for adult patients with common variable immunodeficiency (CVID) in a recently founded adult immunology clinic in the Central Anatolia Region of Turkey, where a clinical immunology center for adults was not available previously.

Materials and methods: A total of 25 patients with CVID aged 18 years and older were included in this study. The file format consisted of 13 pages and was developed for the purpose of the study. Separate sections were designated for identity information, medical history, disease course, previous and current laboratory and imaging studies, follow-up plans, detection and management of complications/comorbidities, and treatment results.

Results: The mean age of the patients was 36.6 ± 13.4 years. The delay in diagnosis was 107 ± 95.6 months. In 92% of patients, initial symptoms resulting in admission to healthcare facilities were infections. Seventeen of 25 patients (68%) had bronchiectasis at the beginning of follow-up.

Conclusion: Early identification of complications and comorbidities in patients with CVID will significantly improve quality of life and survival. Close observation and standardized protocols for follow-up are essential components of management.

Key words: Common variable immunodeficiency, CVID in adults, CVID management, CVID follow-up

1. Introduction

Primary immune deficiencies (PIDs) have been observed in both childhood and adult age groups. The most important issue among adult PID cases is poor awareness, because PIDs are generally considered childhood disorders.

Common variable immunodeficiency (CVID) is a clinically important PID in adult patients. Its prevalence is reported to be 1/10,000–1/50,000 among various populations. In addition to recurrent infections, granulomatous and lymphoproliferative disorders, autoimmunity, and malignancy account for the complex clinical presentation of CVID. Delayed diagnosis and poor management of follow-up are the most important causes of morbidity and mortality associated with this disorder (1–3).

Data from the literature related to the diagnosis and follow-up of PIDs mostly derive from studies performed on pediatric patients. Standardized treatment and follow-up protocols are required to prevent complications, maintain quality of life, and prolong survival in adult patients.

In this study, we present preliminary results from follow-up protocols used in adult CVID patients in a recently founded adult immunology clinic in the Central Anatolia Region of Turkey, where a clinical immunology center for adults was not available previously.

2. Materials and methods

2.1. Patients

CVID patients aged 18 years and over were included in this study. The patients originated from 3 different groups as follows:

1) CVID patients who were still being followed by the Pediatric Immunology Division, despite presently being adults.

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2) Adult CVID patients who were not being followed by any definite clinic and were receiving irregular intravenous immunoglobulin (IVIG) replacement therapy.
3) Adult patients diagnosed with CVID for the first time at our clinic, where this study was conducted.

All patients provided informed consent prior to their inclusion in the study.

2.2. Preparation of the CVID file

A file format consisting of 13 pages was developed for this study. Separate sections were designated for identity information, personal and family medical history, previous disease course, laboratory and imaging study results, follow-up plans, treatment plans, detection and management of complications/comorbidities, and treatment results.

2.3. Collection of retrospective data

All accessible patient files, laboratory results, and electronic epicrises were collected from each patient previously diagnosed with CVID.

2.4. Collection of prospective data

Regular control visits for patients living near the Allergy and Clinical Immunology Division (Konya Province, Turkey) were performed every 3 weeks. For patients residing at distant locations, control visits were performed every 3 months. Patients who did not or could not participate in the control were called to provide the required information (phone visit).

2.5. Standardization of control visits

A special control visit form was prepared for this purpose (Table 1).

Table 1. A standardized form was used at the follow-up visits during this study.

Patient ID : … Date : …
CHECK THE FOLLOWING AT EVERY VISIT: - Any incomplete or lacking laboratory investigation? *No* *Yes (if so, please specify)* - Family screen for PIDs completed? *No* *Yes* - Reaction history on last IVIG infusion? *No* *Yes (if so, please specify)* - Infection episode after last visit (to date)? *No* *Yes (if so, please specify)* - Any current complaints or symptoms? *No* *Yes (if so, please specify)*
FINDINGS OF PHYSICAL EXAMINATION: - Weight/BP/Pulse/Body temperature - Oropharynx : … - Nasal cavity : … - Ears : … - Lungs : … - Abdomen : … - Lymph nodes : … - Other *(please specify)*…
LABORATORY - The last serum IgG level (date and result) … - Laboratory test ordered during this visit (please specify)…
SUMMARY OF THE VISIT - Any newly developed or detected pathologies? *No* *Yes (if so, please specify)* - Replaced IVIG preparation and lot number: *Brand:* *Lot:* - New onset treatments *No* *Yes (if so, please specify)* - Other *(please specify)* NOTES FOR NEXT VISIT- …

2.6. Standardization of laboratory follow-up

Laboratory tests were performed every 3, 6, 12, and 24 months (Table 2). The control chart was generated to monitor completed and pending laboratory investigations and was attached to the first page of the CVID file.

2.7. Standardization of treatment modalities

Standards were determined for intravenous polyclonal immunoglobulin replacement and prophylactic antibiotic treatments based on previous reports (4–6). IVIG doses were reviewed and adjusted specifically for each patient. Staff nurses were trained to perform the IVIG infusion technique. An IVIG infusion protocol, unique for the adult patients, was prepared as a standard order form according to previous reports. All patients were reassessed in terms of the need for prophylactic antibiotics.

2.8. Organization of consultations with related clinics and specialties

Consultations for patients in the pulmonology, gastroenterology, and hematology clinics were performed according to standard protocols. In addition to these specialties, consultations about emerging problems were performed with specialists.

2.9. Patient information

An informational meeting regarding CVID was conducted, since awareness of the disease can increase the efficiency of the treatment and follow-up.

2.10. Consent form for IVIG treatment

An informed consent form for IVIG treatment was prepared and presented to all patients.

2.11. Screening program for CVID on an outpatient basis

Each patient that applied to our outpatient clinic with any complaint was also questioned for infection frequency and immunodeficiency using the "6 ESID Warning Signs for ADULT Primary Immunodeficiency Diseases" (Table 3).

2.12. Family screening for PID

The pedigree of all patients with CVID was issued, and family screening was performed in terms of primary immune deficiency, beginning with the first-degree relatives.

2.13. Physical arrangements in the clinic

An infusion therapy room was established for IVIG replacement. The infusion pump and other necessary equipment and materials were provided.

Table 2. Laboratory tests and intervals during follow-up.

EVERY VISIT (3–4 weeks): Serum IgG level (until reaching a constant trough level, after which it was measured every 3 months) Whole blood counts including hemoglobin, hematocrit, white blood cells, differential, and platelets. Laboratory tests for emerging symptoms and/or complaints (if necessary) Laboratory tests for any chronic pathology that requires follow-up (if existing)
EVERY 3 MONTHS: Serum IgG level Serum levels of BUN, creatinine, sodium, and potassium Urinalysis Stool analysis for ova and parasites
EVERY 6 MONTHS: Serum levels of glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total serum protein, and albumin Autoantibody screen: ANA, anti dsDNA, and thyroid autoantibodies Serum levels of complement components (C3 and C4) Spirometry
ANNUALLY: Thyroid functions including TSH, T4, and T3 tests Tumor markers including CEA, AFP, and CA19-9
BIENNIALLY: High resolution computed tomography (HRCT) Abdominal ultrasonography

Table 3. The 6 ESID warning signs for ADULT primary immunodeficiency diseases.

1	Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, and pneumonia).
2	Recurring infections or infections requiring prolonged antibiotic therapy.
3	Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, and cellulitis).
4	Two or more radiologically proven pneumonia cases within 3 years.
5	Infection with an unusual localization or unusual pathogens.
6	PID in the family.

Source: http://esid.org/Working-Parties/Clinical/Resources/6-Warning-Signs-for-PID-in-Adults.

2.14. Ethical committee approval

The study was conducted after receiving approval from the ethics committee of the Meram School of Medicine, Necmettin Erbakan University.

3. Results

The results of this study are based on 25 CVID patients (13 females/12 males) who were followed between November 2011 and November 2013. The mean age of the patients was 36.6 ± 13.4 years. The age of onset of symptoms was 21.2 ± 17.1 (range: 2–57) years; however, the diagnosis of CVID was established at 30.3 ± 13.8 (range: 10–57) years. The delay in diagnosis was 107 ± 95.6 months (approximately 8 years).

The distribution of adult CVID patients in relation to origin was as follows:

1) Eleven patients who were still being followed by the Pediatric Immunology Division, even though they were adults.
2) Eight patients who were not being followed in any clinic and were receiving irregular IVIG replacement therapy.
3) Six patients diagnosed with CVID for the first time at our recently founded adult immunology clinic.

A total of 14 patients (56%) were residing in Konya, where the study was conducted. The remaining patients (n = 11) visited the clinic from outside the city.

Nine patients were from consanguineous marriages (36%). The daughter of patient 4 (patient 8) was diagnosed with CVID based on a family screening.

A total of 19 patients were married, and 2 female patients had a history of abortion. In 92% of patients, the initial symptoms resulting in admission to healthcare facilities were infections, including upper respiratory tract infections in 3 patients, lower respiratory tract infections in 19 patients, and gastroenteritis in 2 patients. One patient was referred to our clinic due to leg ulcers that were unresponsive to treatment. Nineteen patients (76%) had a history of hospitalization due to recurrent pneumonia. A total of 17 of 25 patients (68%) had bronchiectasis at the beginning of the follow-up.

During the follow-up, 2 patients (patients 8 and 18) became pregnant, both of whom had uncomplicated pregnancies and delivered healthy full-term newborns.

IVIG replacement therapy was administered to all patients with a starting dose of 400–600 mg/kg every 3 weeks. Doses and intervals were adjusted according to the frequency of infection, clinical course, accompanying complications/comorbidities, and trough level of IgG. Among the 421 IVIG replacements performed during the study, only 3 infusion reactions were observed (0.7%).

Existing and newly detected or developed comorbidities/complications during the follow-up period are presented in Table 4 and elaborated on in Section 4.

4. Discussion

CVID is one of the most prevalent PID disorders. It presents a wide variability of symptoms and severities and is clinically the most important PID among adult patients (7,8). The most significant issue in patients with CVID is delayed diagnosis, which ranges from 7.4 to 8.9 years, according to different studies in different populations (1,4,9). In this study, the period between the onset of symptoms and diagnosis was 107 ± 95.6 months (approximately 8 years).

In addition to diagnostic delay, another important issue is how to structure the follow-up protocol of patients. Due to lack of immunoglobulins, CVID cannot simply be defined as a disorder that manifests with recurrent infections. Complications related to infections and autoimmune, granulomatous, gastrointestinal, hematological, and oncological comorbidities form the wide clinical spectrum of CVID. Although some of these problems exist at the time of diagnosis (particularly in cases of delayed diagnosis), the majority tend to occur during the advancing course of the disease (3,4,10,11). Therefore, follow-up after diagnosis is important in this group of patients. However, the existing data on the performance of the clinical follow-up in adult

Table 4. Existing and detected or developed comorbidities/complications in patients with CVID.

Patient	Age	Sex	Complaint	Existing comorbidities and/or complications at the beginning of follow-up	Newly detected or developed comorbidities and/or complications during follow-up
1.	20	M	URTI	None	Bronchiectasis
2.	47	M	URTI	Bronchiectasis, ITP, splenectomy	Chronic sinusitis, atrophic gastritis
3.	26	M	GE	Bronchiectasis	Splenomegaly, anemia, helicobacter pylori infection
4.	35	F	LRTI	Bronchiectasis	Iron-deficiency anemia
5.	53	F	LRTI	Hepatomegaly, CAD, asthma	Atelectasis and other chronic changes in lungs
6.	59	F	GE	Bronchiectasis, HSM, colitis (ulcerative?)	Giardiasis
7.	22	F	LRTI	Bronchiectasis, epilepsy, hepatomegaly	None
8.	27	F	LRTI	Bronchiectasis, splenomegaly	Pregnancy
9.	52	F	LRTI	Splenomegaly	ITP, atelectasis and minimal chronic changes in lungs
10.	60	M	LRTI	CAD	Atopy
11.	27	M	Food ulcer	Bronchiectasis, HSM	Giardiasis
12.	30	F	LRTI	Splenomegaly, bronchiectasis	None
13.	32	M	LRTI	Bronchiectasis	None
14.	25	M	LRTI	Bronchiectasis, HSM	Amyloidosis, nephrotic syndrome, sepsis
15.	21	F	LRTI	Bronchiectasis	Autoimmune thyroiditis
16.	20	F	URTI	None	Systemic lupus erythematosus
17.	30	M	LRTI	Bronchiectasis, HSM, chronic renal failure, amyloidosis	Giardiasis
18.	30	F	LRTI	Bronchiectasis	Pregnancy
19.	61	M	LRTI	Bronchiectasis, splenomegaly, chronic HBV infection	Liver cirrhosis
20.	40	M	LRTI	Splenomegaly	Bilateral hilar lymph node enlargement, chronic sinusitis
21.	39	F	LRTI	Bronchiectasis, chronic HBV infection	Giardiasis
22.	24	M	LRTI	Bronchiectasis, HSM	None
23.	45	M	LRTI	Bronchiectasis, splenomegaly, chronic diarrhea	None
24.	37	F	LRTI	Bronchiectasis, chronic sinusitis	Atopy
25.	53	F	LRTI	Valvular heart disease, heart failure, mediastinal lymphadenopathy	ITP

HSM: Hepatosplenomegaly, ITP: immune thrombocytopenic purpura, CAD: coronary artery disease, URTI: upper respiratory tract infection, LRTI: lower respiratory tract infection, GE: gastroenteritis.

CVID patients are unsatisfactory. The variability in the phenotypes manifested by the disorder among patients affects the patient approaches (12). In this study, we defined standards for long-term follow-up independently of the disease phenotype.

The first step in our effort was to develop a patient file system specific to CVID. The sections and forms of this file were reviewed continually during the course of the study. Incomplete or useless parts were revised to improve the usability of the CVID file. For example, a new form named "case summary", added as "title verso" to the file, was used to summarize the case at a glance. This form consisted of essential information regarding the patient such as complications and/or comorbidities, treatment modalities, infused IVIG brands, infusion reactions (if present), accompanying diseases (if present), and other details not to be overlooked.

Standardization of the follow-up procedures allowed us to make an early diagnosis of certain complications and/or comorbidities and make necessary interventions in time, which are elaborated as follows:

- Patient 1 was diagnosed with CVID at 11 years of age and has been prescribed IVIG replacement therapy since. Unfortunately, his compliance to the treatment was poor, especially based on the timing of IVIG replacement. During the follow-up visits, the patient was reevaluated due to a persistent cough with greenish yellow sputum, and a diagnosis of bronchiectasis was made using high resolution computed tomography (HRCT), whereupon prophylactic antibiotic and mucolytic regimens were initiated along with the IVIG replacement.
- Patient 2 had chronic sinusitis that did not respond to medical treatment. Functional endoscopic sinus surgery was performed since the persistent infection negatively affected the trough level of replaced IgG.
- In patient 14, volume overload (generalized edema) and sustained decreases in serum IgG were observed. Examination revealed the development of nephrotic syndrome as a result of amyloidosis. The IVIG dose and infusion intervals were readjusted according to the levels of serum IgG and proteinuria, and other proper treatments (such as diuretics and colchicine) were initiated after consultation with a nephrology specialist.
- Patient 25 had the complication of persistently decreased platelet counts. Diagnosis of immune thrombocytopenia (ITP), which is the most frequent hematological comorbidity of CVID (1,13), was controlled by an increase in the IVIG dose and corticosteroid treatment. ITP was also observed in patient 9 and was treated with an increased dose of IVIG without corticosteroids.
- In patient 19, who had bronchiectasis, splenomegaly, and chronic HBV infection at the beginning of follow-up, liver cirrhosis was revealed during the follow-up period.
- Systemic autoimmune disease as another common manifestation of CVID (1,14) was observed in 2 female patients during the follow-up: autoimmune thyroiditis in patient 15 and systemic lupus erythematosus (SLE) in patient 16. Autoimmune thyroiditis was diagnosed according to thyroid autoantibody positivity and ultrasonographic findings without any warning symptoms or complaints. However, the patient with SLE had both clinical and laboratory findings, such as ANA and anti-dsDNA positivity, arthralgia, arthritis, malar rash, and photosensitivity.
- Giardiasis was diagnosed in 4 patients as a result of gastrointestinal complaints and routine stool examinations performed at control visits, and the necessary treatments were applied.
- Diagnosis of atopy in patients 10 and 24 allowed us to control upper respiratory tract symptoms using nasal topical corticosteroids.

When we were standardizing the follow-up procedures for CVID, we experienced some difficulties due to the lack of definite literature data and issues with cost-effectiveness. However, we prefer to use cost-benefit issues rather than cost-effectiveness. For example, complete blood count (CBC) tests are recommended every 12 months according to previous studies (2). In our study, we performed CBC tests at every visit (3–4 weeks). Early determination of cytopenias, and especially thrombocytopenia, before they cause complications is important. However, the diagnosis of ITP in 2 patients was based on the persistent decrease in platelets among the CBCs.

Another difficulty encountered during the course of follow-up was convincing the patients to undergo interventional investigations, such as gastrointestinal system (GIS) endoscopy. We performed upper GIS endoscopy in each CVID patient at the beginning of the follow-up and lower GIS endoscopy in patients experiencing lower GIS complaints (15–17). We could not convey the importance and necessity of GIS endoscopy to the majority of CVID patients, who only complained about recurrent infections. Therefore, because of the limited number of patients, it was not possible to interpret the GIS endoscopic results.

Autoantibody positivity alone was not valuable for the diagnosis of autoimmunity in patients already receiving IVIG; thus, semiannual autoantibody screening was forsaken during the advancing course of the study and was performed only on patients showing clinical signs and symptoms of autoimmune disorders.

Bronchiectasis is one of the most important complications determining mortality and morbidity in patients with CVID. In the majority of centers, the first-line imaging study to monitor progression of bronchiectasis is HRCT. However, there are some drawbacks to using HRCT due to chromosomal radiosensitivity in CVID (1,18). Clear data regarding the total radiation dose and frequency of exposure are not available. Alternatively, there are some studies that propose the use of lung MRI imaging to diagnose bronchiectasis. However, data on the usefulness of lung MRI in monitoring the progression of bronchiectasis are limited (19). In our study, only HRCT was used to follow patients with bronchiectasis.

In conclusion, our results indicated that due to limitations in the number of patients and study duration, close observation and standardized protocols for follow-up are essential components of the management of adult CVID patients. Early identification of complications and comorbidities will provide significant improvements in quality of life and survival. As in all disorders with chronic courses, we require a well-adapted patient file system and protocols for the long-term management of adult patients with CVID.

References

1. Yong PF, Thaventhiran JE, Grimbacher B. 'A rose is a rose is a rose,' but CVID is not CVID: Common variable immune deficiency (CVID), what do we know in 2011? Adv Immunol 2011; 111: 47–107.
2. Cunningham-Rundles C. How I treat common variable immune deficiency. Blood 2010; 116: 7–15.
3. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119: 1650–1657.
4. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, Claudio P, Franco D, Pesce AM, Borghese F et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007; 27: 308–316.
5. Shehata N, Palda V, Bowen T, Haddad E, Issekutz TB, Mazer B, Schellenberg R, Warrington R, Easton D, Anderson D et al. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. Transfus Med Rev 2010; 24: 28–50.
6. Detková D, Español T. An update on treatment strategies for common variable immunodeficiency. Exp Rev Clin Immunol 2009; 5: 381–390.
7. Kumar Y, Bhatia A. Common variable immunodeficiency in adults: current diagnostic protocol and laboratory measures. Exp Rev Clin Immunol 2013; 9: 959–977.
8. García JM, Gamboa P, de la Calle A, Hernández MD, Caballero MT, García BE, Labrador M, Lahoz C, Longo Areso N, López Hoyos M et al. Diagnosis and management of immunodeficiencies in adults by allergologists. J Invest Allerg Clin 2010; 20: 185–194.
9. Ardeniz O, Başoğlu OK, Günşar F, Unsel M, Bayraktaroğlu S, Mete N, Gülbahar O, Sin A. Clinical and immunological analysis of 23 adult patients with common variable immunodeficiency. J Invest Allerg Clin 2010; 20: 222–236.
10. Maarschalk-Ellerbroek LJ, Hoepelman AI, van Montfrans JM, Ellerbroek PM. The spectrum of disease manifestations in patients with common variable immunodeficiency disorders and partial antibody deficiency in a university hospital. J Clin Immunol 2012; 32: 907–921.
11. Ballow M. Managing comorbid complications in patients with common variable immunodeficiency. Ann Allerg Asthma Im 2013; 111: 6–9.
12. Jolles S. The variable in common variable immunodeficiency: a disease of complex phenotypes. J Allergy Clin Immun 2013; 1: 545–556.
13. Podjasek JC, Abraham RS. Autoimmune cytopenias in common variable immunodeficiency. Front Immunol 2012; 24: 189.
14. Abolhassani H, Amirkashani D, Parvaneh N, Mohammadinejad P, Gharib B, Shahinpour S, Hirbod-Mobarakeh A, Mirghorbani M, Movahedi M, Gharagozlou M et al. Autoimmune phenotype in patients with common variable immunodeficiency. J Invest Allerg Clin 2013; 23: 323–329.
15. Agarwal S, Mayer L. Gastrointestinal manifestations in primary immune disorders. Inflamm Bowel Dis 2010; 16: 703–711.
16. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007; 31: 1800–1812.
17. Dhalla F, da Silva SP, Lucas M, Travis S, Chapel H. Review of gastric cancer risk factors in patients with common variable immunodeficiency disorders, resulting in a proposal for a surveillance programme. Clin Exp Immunol 2011; 165: 1–7.
18. Aghamohammadi A, Moin M, Kouhi A, Mohagheghi MA, Shirazi A, Rezaei N, Tavassoli S, Esfahani M, Cheraghi T, Dastan J et al. Chromosomal radiosensitivity in patients with common variable immunodeficiency. Immunobiology 2008; 213: 447–454.
19. Serra G, Milito C, Mitrevski M, Granata G, Martini H, Pesce AM, Sfika I, Bonanni L, Catalano C, Fraioli F et al. Lung MRI as a possible alternative to CT scan for patients with primary immune deficiencies and increased radiosensitivity. Chest 2011; 140: 1581–1589.