Different clinical phenotypes in common variable immunodeficiency

Heterogeneity of common variable immunodeficiency

Maíra Ribeiro Rodero, Marina Benevides, Barbara Maximo Nascimento, Helena de Almeida Secchi, Persio Roxo-Junior

Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

Manuscript accepted for publication

Summary

Background. We aimed to describe the clinical heterogeneity (infectious and noninfectious manifestations) and the impact of immunoglobulin replacement therapy on the reduction of infections in patients given a diagnosis of common variable immunodeficiency. **Methods.** This was a descriptive case series study. Medical charts were retrospectively reviewed based on demographics, clinical presentation, immunoglobulin replacement therapy and laboratory findings at diagnosis. **Results.** Thirty six common variable immunodeficiency patients were enrolled. Nineteen of them were male (53%). The median age at onset of symptoms was 8 years and at common variable immunodeficiency diagnosis was 19 years. Family history for immunodeficiency was observed in 2 patients (5%). Recurrent infections were present in 35 patients (97%) and they were the first clinical manifestations in 31 patients (86%). Respiratory infections were the most frequent, followed by gastrointestinal infections. Noninfectious manifestations were present in 32 patients (89%), including bronchopulmonary disease, allergy, autoimmunity, lymphoproliferation, gastrointestinal disorders and malignancy. Chronic pulmonary disease and lymphoproliferation were the most common. There was an important reduction of infections 1 year after begining immunoglobulin replacement therapy, mainly pneumonia and sinusitis. **Conclusions.** Although the diagnosis of common variable immunodeficiency has improved over the last decade, many patients are still being referred and diagnosed late. Physicians must recognize that both infectious and noninfectious manifestations

can be the initial signs of common variable immunodeficiency and are very common in these patients. Immunoglobulin replacement therapy significantly reduces respiratory infections.

Key words

Common variable immunodeficiency; primary immunodeficiency diseases; infections; immunoglobulins; inflammation.

IMPACT STATEMENT

Common variable immunodeficiency is a very complex and heterogeneous disease, characterized by hypogammaglobulinemia, leadind to recurrent infectious, and noninfectious complications including immune dysregulation, autoimmunity, hematological, pulmonary and gastrointestinal manifestations.

Introduction

Common variable immunodeficiency (CVID) represents the most common symptomatic inborn error of immunity (IEI) in adults (1). The estimated prevalence in the general population is 1:50.000 to 1:25.000 (2). The disease is characterized by significant decrease in the serum concentration of IgG associated with, usually a low IgA, and often a low IgM, and impaired antibody response to vaccination, in patients in whom other causes of humoral immunodeficiency are ruled out (3).

The severe hypogammaglobulinemia leads to recurrent infections, especially of the respiratory tract. However, the disease is also associated with noninfectious manifestations like granulomas, chronic lung disease, generalized lymphoid hypertrophy, splenomegaly, gastrointestinal disease, malignancy and cytopenias, amongst other inflammatory manifestations (4-7).

This wide clinical heterogeneity has led to diagnostic challenges and difficulties in the development of optimal treatment plans for patients with CVID, contributing to late diagnosis and increase of chronic complications and lethality (8).

Manuscript accepted for publication

In this perspective, the knowlege of the heterogeneous clinical picture by the physicians is essential to early suspicion of CVID. In this study, we aimed to describe the clinical features of the infectious and noninfectious manifestations in CVID patients and to evaluate the impact of immunoglobulin replacement therapy (IgRT) on the reduction of infections.

Methods

Study design

This was a descriptive and retrospective case series study that evaluated CVID patients followed at the Division of Immunology and Allergy, Department of Pediatrics of Ribeirão Preto Medical School, University of São Paulo. All data for this study represented a 23-year cumulative experience and were collected between 2000 and 2023.

Subjects

Patients were eligible for enrollment in the study if they had a CVID diagnosis based on the 2019 ESID criteria (9).

Patients under age 4 years and who were followed irregularly or missed follow-up care were excluded.

Data collection

Data were reviewed for each patient from their medical records, based on the following data: population demographics; clinical presentation (age at onset of symptoms and at diagnosis, family history for IEI, consanguinity, type of infections, noninfectious manifestations, hospitalisations, deaths); IgRT and laboratory findings (serum immunoglobulin levels at diagnosis and peripheral blood lymphocytes subsets).

In this study, the criteria for recurrent infections were defined by the authors based on the annualized rate for each type of infection: >3 episodes of acute pharyngo-tonsillitis; >4 episodes of acute otitis media; >3 episodes of acute sinusitis; >2 episodes of pneumonia; >3 episodes of diarrhea.

Manuscript accepted for publication

Ethical Considerations

This study was approved by the local Research Ethics Committee (CAAE 14303613.0.0000.5440) and was conducted following the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Results

Population demographics

Thirty six CVID patients were included in the study. Nineteen of them were male (53%). One patient was African American; the rest were Caucasian (97%).

The median age at CVID diagnosis was 19 years of life (7 - 65).

Family history of presumptive diagnosis of CVID was observed in 2 patients (5%), genetic test was not performed. Parental consanguinity was found in 1 patient (3%).

Clinical manifestations

Recurrent infections occurred in 35 patients (97%); 31 patients (86%) presented these manifestations at onset. The median age at onset of infections was 8 years (1 – 49). Respiratory infections were the most frequent, followed by gastrointestinal infections. Associated respiratory and gastrointestinal infections were reported in 8 patients (23%). Isolation of the pathogen was positive in 10 patients (28%), and the isolated agents were *Giardia lamblia* (5 patients), *S. pneumoniae* (3 patients), *Cryptococcus neoformans* and *S. aureus* (1 patient) and *Klebsiella sp* (1 patient). Thirty patients (83%) were hospitalysed due to infections.

Noninfectious manifestations were present in 32 patients (89%), including bronchopulmonary disease, allergy, autoimmunity, lymphoproliferation, gastrointestinal disorders and malignancy. The median age at onset of these complications was 29 years (10 – 59). The most common manifestations were chronic pulmonary disease and lymphoproliferation, which were found together in 29 patients (90%). Autoimmunity was the first clinical manifestations in 2 patients

Manuscript accepted for publication

(6%), presenting as juvenile idiopathic arthritis and alopecia areata. The rest of noninfectous complications occurred during follow up. The clinical findings are summarised in Table I.

Outcome

Three patients (8%) have died, with a median age of death of 32 years-old (22 - 45). The causes of death were pneumonia (2 patients) and liver failure secondary to primary biliary cholangitis (1 patient).

Diagnostic delay greater than 5 years was associated with deaths and hospitalizations.

IgRT

All patients received IgRT either in intravenous (IVIgRT) or subcutaneous (SCIgRT) form; 30 patients (83%) received IVIgRT (mean dosis was 600mg/kg each 3 weeks) and 6 patients (17%) received SCIgRT (mean dosis was 180mg/kg weekly). The average serum IgG levels after 1 year of treatment were 920mg/dL for IVIgRT and 1080mg/dL for SCIgRT; both were correlated with an important reduction of infections, especially pneumonia and sinusitis ($p < 0.04$). The Figure 1 shows the percentage of patients with recurrent pneumonia and sinusitis before IgRT and 1 year after begining treatment.

However, IgRT did not reduce the occorrence of noninfectious complications.

Laboratory findings

All subjects in this cohort presented reduced levels of IgG, IgM and IgA. The median baseline levels were: IgG 158 mg/dL (0,44 - 673); IgM 17 mg/dL (0,5 - 117) and IgA 10 mg/dL (3,2 - 58,4); IgG levels less than 250 mg/dL were correlated with severity of infections (measured by number of hospitalization).

Absolute CD3, CD4, CD8 T cells, and CD19 B lymphocyte numbers were numbers were reduced in 12 patients (33%), 3 patients (8%) and 22 patients (61%), respectively. The median numbers were: CD4 338/μL (324 – 354); CD8 677/μL (648 - 1924) and CD19 148/μL (27 - 679). T and B-cell functional assays and specific lymphocyte markers were not performed.

Manuscript accepted for publication

Discussion

CVID is characterized as a clinical syndrome representing a heterogenous group of disorders that exhibits hypogammaglobulinemia and infections. Patients with CVID can be grouped into 2 categories: one group that exhibits hypogammaglobulinemia without other noninfectious complications, and a second group with autoimmunity and inflammatory complications (5).

In this study we characterized the infectious and noninfectiouns manifestations in 36 CVID patients, as well as the impact of IgRT on the reduction of infections.

The median age at onset of symptoms was 8 years, and at CVID diagnosis was 19 years of life, representing a diagnostic delay of 11 years, similar to other studies (2,10), although some authors described a lower diagnostic delay, ranging from 7 to 9 years (11,12). The high diagnostic delay observed in our study could be related to the fact that immunodeficiencies are not usually suspected in adults and first symptoms were considered banal respiratory infections by patients and doctors (11).

In our study, 5% of patients presented family history for IEI, similar to other studies (5,10).

Acute and chronic infections are the most common clinical manifestation and a hallmark feature of CVID. In this study, recurrent infections were reported in almost all patients and they were the first clinical manifestations in 86% of them. Similar to our findings, Cunningham-Rundles *et al*. (5) evaluated a cohort of 248 CVID patients and they related that 98% of this group presented recurrent infections. Oksenhendler *et al*. (11) evaluated 252 CVID patients and they described that recurrent infections were the first clinical presentation in all patients.

Among the infections, we found that the respiratory tract involvement was the most frequent, especially pneumonia and sinusitis, as reported by other studies (5,11,13,14). On the other hand, Quinti *et al*. (12) described pneumonia just in 49% of patients. Such differences can be explained by different criteria used to diagnose infections. The most common organisms involved in respiratory infections are encapsulated bacteria (eg, *H. influenzae* and *S. pneumoniae*) (14). We identified *S. pneumoniae* in 3 patients, all of them with pneumonia.

Manuscript accepted for publication

In this study, diarrhea was the second most frequent infection, affecting 44% of patients, similarly to Fernández Romero *et al*. (10) and Oksenhendler *et al*. (11), who observed diarrhea in 41% and 47% of patients, respectivelly.

Opportunistic infections are usually uncommon in CVID patients. Lucas *et al*. (15) evaluated prospectively a cohort of 90 CVID patients and they identified opportunistic infections in less than 10% of patients. We identified opportunistic infection in just 1 patient, who presented encephalitis by *Cryptococcus neoformans*.

One interesting point of our study was the high rate of hospitalizations due to infections, reinforcing the role of infections as an important cause of morbidity and mortality.

IgRT is considered as the "gold standard" treatment and plays an important role in reducing and preventing severe infections as well as improving survival in CVID patients (16,17). As expected, we found an important reduction of respiratory infections 1 year after begining IgRT, especially for pneumonia and sinusitis. However, despite IgRT, some patients still experienced noninfectious complications, similarly as described by Poto *et al*. (16)

CVID is also commonly associated with noninfectious and inflammatory complications, leading to chronic lung disease, generalized lymphoid hypertrophy, splenomegaly, gastrointestinal disease, and cytopenias, amongst other inflammatory manifestations (3,14). In our study, the noninfectious manifestations were present in most of patients, especially chronic pulmonary disease and lymphoproliferation (50% and 47%, respectivelly).

Among the pulmonary diseases, bronchiectasis were present in more than half of our patients, similarly to other studies (10,19). Interstitial lung disease (ILD) is a term that encompasses a group of different acute and chronic pulmonary conditions with common clinical and physiological characteristics. The diagnosis of ILD is commonly made based on clinical presentation and includes histologic aspects and computed tomography (18). In this study, ILD was the second main respiratory manifestation, committing 11% of our patients; all of them were confirmed by biopsy and computerized tomography scans of the chest. Lopes *et al*. (3) evaluated a CVID patients' cohort and they reported a 10% overall frequency of ILD, similar to other reports in which the incidence ranges from 10 to 20% (20,21).

Manuscript accepted for publication

Forty seven percent of our patients had some type of lymphoproliferation; among them splenomegaly was the most frequent (44%). This high rate was similar to other European series, that report a rate up to 66% of patients (6,11,12). Lymphoproliferative disease and increased susceptibility toward development of malignancy can occur in patients with impaired immune function. In this study no patients presented malignancy associated to lymphoproliferation. However, it is strongly recommended that CVID patients with lymphoproliferation be monitored periodically.

Autoimmune conditions are a common presentation in CVID, present in 25% to 30% of patients (22,23). Among these manifestations, autoimmune hematologic conditions are the most common, thought to be secondary to underlying immune dysregulation associated with CVID (14). In this study, autoimmunity was found in 28% of the patients; cytopenias and hypothyroidism were the most frequent autoimmune diseases.

As a similar way, allergy can be also secondary to dysregulation, as evidenced by high rates of atopy in patients with CVID (5). Khaled *et al*. (24) evaluated 36 CVID patients and they reported a 31% rate of allergy. Forty four percent of our patients had some allergic disease, especially allergic rhinitis.

Gastrointestinal commitment is a common complication associated with CVID, including variable clinical presentation like villous atrophy, chronic exudative enteropathy, chronic enteritis/colitis and liver disease (14). In this study, we found a 42% rate of gastrointestinal disorders, especially chronic hepatitis. Khaled *et al*. (24) reported gastrointestinal diseases in 75% of their cohort.

This study has some limitations. First, the low number of patients, but it was conducted in a single center and CVID is considered a rare disease. In addition, the retrospective design. Despite these limitations, our study showed the importance of IgTR in the reduction of respiratory infections and the high rate of noninfectious complications in CVID patients, which are often under-diagnosed in developing countries.

We conclude that although the diagnosis of common variable immunodeficiency has improved over the last decade, many patients are still being referred and diagnosed late. Physicians must

Manuscript accepted for publication

recognize that both infectious and noninfectious manifestations can be the initial presentation of common variable immunodeficiency and are very common in these patients. IgRT significantly reduces respiratory infections, improving the prognosis and quality of life. Further multicenter studies focusing on the heterogeneous clinical presentation in the Brazilian population are needed.

Fundings: None

Conflicts of interest: None

Consent Statement: Written informed consent were obtained from the patients for the publication of any images or data included in this article.

Acknowledgements: None.

Contributions: MRR - Conceptualization, Methodology, Investigation, Writing (original draft); MB - Investigation, Writing (original draft); BMN - Investigation, Writing (original draft), Figure edition; HAS - Investigation, Writing (original draft), Table edition; PRJ - Conceptualization, Methodology, Investigation, Writing (original draft), Writing (review & editing), Supervision.

Manuscript accepted for publication

References

1. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2016;4(1):38–59. doi: 10.1016/j.jaip.2015.07.025.

2. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134:116–126. doi: 10.1016/j.jaci.2013.12.1077.

3. Lopes J, Ho H, Cunningham-Rundles C. Interstitial Lung Disease in Common Variable Immunodeficency. Front Immunol 2021; 12:605945. doi: 10.3389/fimmu.2021.605945.

4. Baloh C, Reddy A, Henson M, Prince K, Buckley R, Lugar P. 30-Year Review of Pediatric and Adult-Onset CVID: Clinical Correlates and Prognostic Indicators. J Clin Immunol. 2019;39(7):678-687. doi: 10.1007/s10875-019-00674-9.

5. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999; 92:34-48. doi: 10.1006/clim.1999.4725.

6. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common Variable immunodeficiency disorders: Division into distinct clinical phenotypes. Blood. 2008; 112:277-286. doi: 10.1182/blood-2007-11-124545.

7. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650-1657. doi: 10.1182/blood-2011-09-377945.

8. Lopes JP, Cunningham-Rundles C. The Importance of Primary Immune Deficiency Registries: The United States Immunodeficiency Network Registry. Immunol Allergy Clin N Am 2020;40 (3): 385–402. doi: 10.1016/j.iac.2020.03.002.

9. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J et al. The European Society for Immunodeficiencies (ESID) Registry working definitions for the clinical

Manuscript accepted for publication

diagnosis of inborn errors of immunity. J Allergy Clin Immunol Pract 2019;7(6):1763–1770. doi: 10.1016/j.jaip.2019.02.004.

10. Fernández Romero DS, Juri MC, Paolini MV, Malbrán A. Common variable immunodeficiency. Epidemiology and clinical manifestations in 69 patients. Medicina (B Aires) 2013;73(4):315-323.

11. Oksenhendler E, Gérard L, Fieschi C, et al. Infections in 252 patients with Common Variable Immunodeficiency. Clinical Infectious Diseases 2008; 46: 1547-1554. doi: 10.1086/587669.

12. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. Journal of clinical immunology. 2007;27(3):308-316. doi: 10.1007/s10875-007-9075-1.

13. Salehzadeh M, Aghamohammadi A, Rezaei N. Evaluation of Immunoglobulin Levels and Infection Rate in Patients with Common Variable Immunodeficiency After Immunoglobulin Replacement Therapy. J Microbiol Immunol Infect. 2010;43(1):11-17. doi: 10.1016/S1684-1182(10)60002-3.

14. Remiker A, Bolling K, Verbsky J. Common Variable Immunodeficiency. Med Clin North Am. 2024;108(1):107-121. doi: 10.1016/j.mcna.2023.06.012.

15. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J Allergy Clin Immunol. 2010;125(6):1354-1360. doi: 10.1016/j.jaci.2010.02.040.

16. Poto R, Pecoraro A, Ferrara AL, Punziano A, Lagnese G, Messuri C. et al. Cytokine dysregulation despite immunoglobulin replacement therapy in common variable immunodeficiency (CVID). Front Immunol. 2023;14:1257398. doi: 10.3389/fimmu.2023.1257398.

17. Jolles S, Chapel H, Litzman J. When to initiate immunoglobulin replacement therapy (IGRT) in antibody deficiency: a practical approach. Clin Exp Immunol 2017; 188(3):333–341. doi: 10.1111/cei.12915.

Manuscript accepted for publication

18. Baumann U, Routes JM, Soler-Palacin P, Jolles S. The Lung in Primary Immunodeficiencies: New Concepts in Infection and Inflammation. Front Immunol 2018;9: 1837. doi: 10.3389/fimmu.2018.01837.

19. Maarschalk-Ellerbroek LJ, de Jong PA, van Montfrans JM, Lammers J, Bloem AC, Hoepelman AI et al. CT screening for pulmonary pathology in common variable immunodeficiency disorders and the correlation with clinical and immunological parameters. J Clin Immunol 2014; 34(6):642–654. doi: 10.1007/s10875-014-0068-6.

20. Kellner ES, Fuleihan R, Cunningham-Rundles C, Consortium U, Wechsler JB. Cellular defects in CVID patients with chronic lung disease in the USIDNET registry. J Clin Immunol. 2019; 39:569–576. doi: 10.1007/s10875-019-00657-w.

21. Hanitsch LG, Wittke K, Stittrich AB, Volk HD, Scheibenbogen C. Interstitial lung disease frequently precedes CVID diagnosis. J Clin Immunol. 2019; 39:849–851. doi: 10.1007/s10875-019-00708-2.

22. Agarwal S, Cunningham Rundles C. Autoimmunity in common variable immunodeficiency. Ann Allergy Asthma Immunol 2019;123(5):454-460. doi: 10.1016/j.anai.2019.07.014.

23. Mormile I, Punziano A, Riolo CA, Granata F, Williams M, de Paulis A et al. Common variable immunodeficiency and autoimmune disease: a retrospective study of 95 adult patients in a single tertiary care center. Front Immunol 2021;12:652487. doi: 10.3389/fimmu.2021.652487.

24. Khaled MB, Merdassi A, Rekaya S, Fraj IB, Lamouchi T, Zaiter I et al. Clinical features and predictors of osteoarticular manifestations in common variable immunodeficiency. Clin Rheumatol. 2023;42(11):3123-3129. doi: 10.1007/s10067-023-06722-5.

Manuscript accepted for publication

Table I. Clinical findings encountered in the CVID patients.

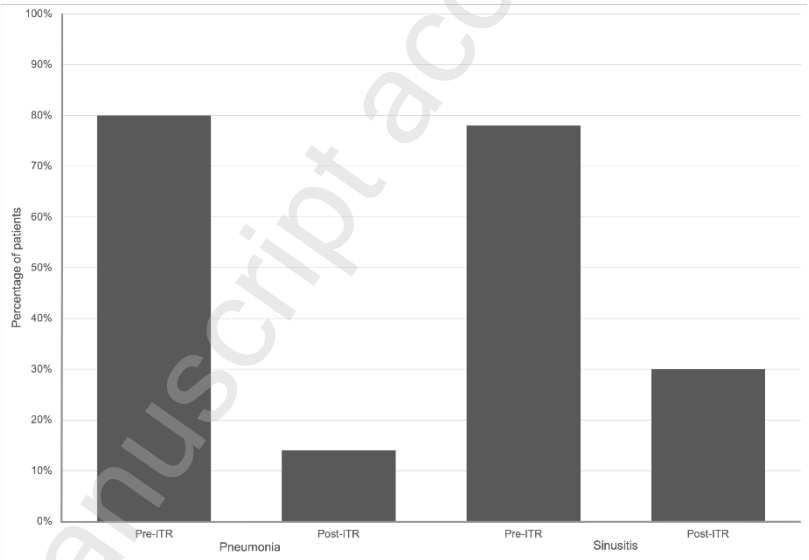
Data	Number of patients (%)
Consanguinity	1 (3)
Family history for IEI	2 (5)
Infections manifestations	35 (97)
Pneumonia	29 (80)
Sinusitis	28 (78)
Tonsillitis	13 (36)
Acute otitis media	9 (25)
Diarrhea	16 (44)
Sepsis	9 (25)
Skin	7 (19)
Encephalitis	5 (14)
Noninfectious manifestations	32 (89)
Pulmonary disorders	18 (50)
Bronchiectasis	17 (47)
ILD*	4 (11)
Lymphoproliferation	17 (47)
Splenomegaly	16 (44)
Hepatomegaly	8 (22)
Adenomegaly	7 (19)
Autoimmunity	10 (28)
Hashimoto	3 (8)
Sicca syndrome	2 (5)
Alopecia areata	1 (3)
Juvenile idiopathic arthritis	1 (3)

Manuscript accepted for publication

Primary biliary cholangitis	1 (3)
Celiac disease	1 (3)
Hemolytic anemia	1 (3)
Immune thrombocytopenia	2 (5)
Allergy	16 (44)
Allergic rhinitis	12 (33)
Asthma	4 (11)
Gastrointestinal disorders	15 (42)
Chronic hepatitis	7 (19)
Chronic diarrhea	5 (14)
Chronic colitis	2 (5)
Malignancy	2 (5)

* ILD: Interstitial lung disease.

Figure 1. Impact of IgRT on infections (1 year after begining) in the CVID patients.



Manuscript accepted for publication