Immunol Genet J, Vol. 4, No. 2, June 2021, pp.87-94 **DOI: https://doi.org/10.18502/igj.v4i2.9984**

Original Article

Cardiac Complications in Patients with Common Variable Immune Deficiency: A Longitudinal Study

Nasim Ramzi[1,2], Shahrooz Yazdani[3], Hamed Talakoob[3], Seyed Erfan Rasouli[4], Hossein Karim[4*], Gholamreza Azizi[4*]

[1] *Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran*
[2] *Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Cardiovascular Research Center, Alborz University of Medical Sciences, Karaj, Iran*
[4] *Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran*

Received: 05 April 2021; Accepted: 12 May 2021

Abstract

Background: The common variable immune deficiency (CVID) is known as the most prevalent symptomatic primary immune deficiency (PID) diseases, which is characterized by hypogammaglobulinemia with variable infectious and noninfectious manifestations. In this study, the researchers aimed to evaluate the frequency of cardiac disorders and investigate its association with other manifestations in CVID patients.

Method: A total of 337 CVID patients registered in the Iranian Primary Immunodeficiency Registry were evaluated in this study. The questionnaire was completed for all patients to collect the participants' demographic data, clinical manifestations and laboratory finding. The analysis was performed between the two groups of the study including CVID patients with cardiac manifestation and those without it.

Results: The prevalence rate of cardiac manifestation was calculated to be 9.1%. pericardial and myocardial diseases and pulmonary hypertension were the most prevalent complications. CVID patients with a history of cardiac problem had significantly higher prevalence rates of otitis media, lymphoproliferative disorders, splenomegaly, hepatomegaly, failure to thrive and lower numbers of CD8+ T cells and CD19+ B cells compared to the patients without cardiac disorders. Notably, no significant differences were observed in immunoglobulins serum levels, CD3+ and CD4+ T cells between the patients with and without cardiac manifestation.

Conclusion: Regular echocardiographic evaluation and of CVID patients for cardiac complications especially for inflammatory cardiac disease, heart failure and pulmonary hypertension, is critical to reduce the risk of heart disease.

Keywords: Common Variable Immune Deficiency; Cardiac Disorders; Clinical Manifestations; Autoimmunity; Pericardial Disease

***Corresponding Authors:** Hossein Karim, MD
Cardiovascular Research Center, Alborz University of Medical Sciences, Karaj, Iran
E-mail: dr_karim@kums.ac.ir

Gholamreza Azizi, PhD
Non-communicable Diseases Research Center, Vice Chancellor for Research, Alborz University of Medical Sciences, Karaj, Iran
E-mail: azizi@abzums.ac.ir

How to cite this article
Ramzi N, Yazdani S, Talakoob H, Rasouli SE, Karim H, Azizi G. Cardiac Complications in Patients with Common Variable Immune Deficiency: A Longitudinal Study. Immunology and Genetics Journal, 2021; 4(2): 87-94. DOI: https://doi.org/10.18502/igj.v4i2.9984

Introduction

Common variable immune deficiency (CVID) is one of the most common symptomatic primary immunodeficiency (PID) (1). CVID characterized by hypogammaglobulinemia and poor antibody responses to antigens (2). It has approximate incidence of 1:50,000-1:25,000 (3). CVID has a broad range of manifestations; recurrent bacterial infections especially upper and lower respiratory tract infections which are the most typical clinical manifestations, others include autoimmunity (of which autoimmune cytopenias are the most common), enteropathy, lymphoproliferative disorders, malignancy and allergic diseases (4).

Among different clinical manifestations, cardiovascular abnormalities are not common in CVID (5), and there are few reports of cardiac disorders in CVID. Chronic pulmonary complications such as bronchiectasis due to recurrent respiratory tract infections predispose CVID patients to pulmonary hypertension (6). Acute pericarditis and pericardial effusion are reported in CVID which can be caused by infections or autoimmunity (7, 8). Myocarditis and aortic aneurysm are another reported complications in CVID patients (9, 10).

In this study, the researchers aimed to evaluate the frequency of cardiac manifestations and types of cardiac disorders among CVID patients. They also aimed to compare demographic data, clinical manifestations and immunological characteristics in patients with and without cardiac disorders.

Patients and Methods

The researchers retrospectively reviewed medical data of 337 CVID patients registered in the Iranian Primary Immunodeficiency Registry (11) at children's medical center hospital, Tehran, Iran between 1999 and 2020. The CVID was diagnosed according to the criteria of the European Society for Immunodeficiencies (ESID) Registry working party (12). A questionnaire was completed for all patients to record demographic data, clinical and laboratory data, past medical history of cardiac manifestation and other complications. The research protocol was approved by the institutional Ethics review committee. The researchers extracted the medical records of CVID patients diagnosed with any cardiac problems such as any complaint of chest pain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), syncope, palpitation, any finding in examination like abnormal heart sound, any finding in electrocardiography and echocardiography or any imaging abnormality in favor of cardiac disorder.

Statistical analysis

The statistical values such as frequency (number and percentage) and median (interquartile range, IQR) were used. For comparisons between two groups of patients, Mann-Whitney U, Fisher's exact and chi-square tests were applied. For doing parametric and non-parametric tests, the researchers evaluated the normality assumption for a variable with Shapiro-Wilks tests. All statistical tests were two-tailed, and P-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Baseline demographic data

A total of 337 CVID patients (192 male [56.9%] and 145 female [43.1%]) with a median (IQR) age at diagnosis of 120.0 (36.0-252.0) months were enrolled in this study. The patient's data are summarized in **Table 1**. 31 patients (9.1%) with cardiac manifestations were found. The researchers categorized cardiac manifestations of the patients into six groups which contain myocardial diseases including myocarditis and cardiomyopathies such as heart failure, valvular heart diseases, pericardial diseases, congenital heart diseases, arrhythmia and pulmonary hypertension (13-19). Cardiac complications of nine patients were not fully followed-up and the researchers found reports of complaints such as chest pain, dyspnea or palpitation or reports of murmurs in heart sounds or a cardiomegaly in chest radiography, or having echocardiographic finding which did not indicate a specific disorder, for example; brief dilatation of the cardiac chambers, Trivial valvular insufficiency. As a result, the researchers put these patients in the group of other manifestations. Five patients had experienced more than one cardiac disorder. Consanguinity was found among 179 (53.1%) of the CVID patients, 18 (58.1%) (p=0.923) patients of whom had a manifestation of cardiac disease. Among the patients with cardiac problems, 15

Table 1. Demographic and immunological data for CVID patients at the time of diagnosis

Parameters	Total (n=337)	Patients without cardiac manifestations (n=306)	Patients with cardiac manifestations (n=31)	*P*-value
Gender, M/F, (n=337)	192/145	177/129	15/16	0.311
Consanguinity (%), (n=337)	179(53.1%)	161(52.6%)	18(58.1%)	0.923
Age at the study time (years), median (IQR), (n=278)	24.0 (15.0-33.0)	24.0 (15.0-34.0)	22.0 (14.0-30.0)	0.417
Age at onset (months), median (IQR), (n=307)	24.0 (6.0-84.0)	24.0(6.0-96.0)	24.0 (4.50-64.50)	0.440
Age at diagnosis (months), median (IQR), (n=309)	120.0 (36.0-252.0)	120.0(36.0-273.0)	72.0(21.0-138.0)	0.060
Diagnostic delay (months), median (IQR), (n=295)	48.0(12.0-108.0)	48.0(16.0-120.0)	36.0(9.50-63.00)	0.068
WBC (cell/µl), median (IQR), (n=318)	7800.0(5400.0-10785.0)	8000.0(5600.0-11000.0)	6780.0(2300.0-10400.0)	*0.040**
Lymphocyte (cell/µl), median (IQR), (n=307)	2471.00(1672.25-4198.50)	2497.50(1725.00-4244.75)	1883.50(1016.00-3461.00)	0.083
Neutrophil (% of total WBC), median (IQR), (n=298)	55.00(41.98-67.00)	55.00(43.00-67.00)	48.00(37.75-65.75)	0.296
IgG (mg/dl), median (IQR), (n=337)	211.50 (47.25-471.25)	210.00(55.00-475.00)	270.00(17.00-463.00)	0.729
IgA (mg/dl), median (IQR), (n=337)	14.00 (4.00-42.00)	13.00(4.00-42.00)	18.00(10.00-45.25)	0.277
IgM (mg/dl), median (IQR), (n=337)	26.00 (9.00-50.00)	26.50(9.00-52.25)	19.00(12.00-36.00)	0.390
IgE (IU/mL), median (IQR), (n=209)	1.50 (0.10-6.00)	1.61(0.70-6.00)	1.00(0.00-14.00)	0.459
CD3+ T cells (cell/µl), median (IQR), (n=279)	1800.00(1293.00-3105.50)	1846.00(1328.50-3153.00)	1596.00(586.75-2626.00)	0.146
CD4+ T cells (cell/µl), median (IQR), (n=281)	798.00(437.50-1479.50)	805.00(446.75-1475.25)	600.00(322.00-1497.00)	0.132
CD8+ T cells (cell/µl), median (IQR), (n=275)	930.00(585.00-1575.75)	954.00(598.00-1622.00)	735.00(224.00-1075.50)	*0.020**
CD19+ B cells (cell/µl), median (IQR), (n=266)	216.00(78.00-535.00)	246.96(84.66-583.00)	130.50(47.25-346.10)	*0.040**

The median is shown (with IQR, 25th, and 75th percentiles)

n, number; Ig, immunoglobulin; WBC, white blood cell; CD, cluster of differentiation.

**P*-value is statistically significant < 0.05

(48.4%) cases were men and 16 (51.6%) subjects were women. The analysis revealed that the median age of the patients at the diagnosis of immunodeficiency was 120.0 months for the patients without cardiac disorders and 72.0 months for the patients with cardiac disorders (p = 0.060).

Clinical evaluation

The researchers categorized 31 patients' cardiac manifestations into seven groups (**Table 2**). Patients in the category of congenital heart defects had atrial septal defect (ASD) (3 patients) and ventricular septal defect (VSD) (1 patient). Heart

Table 2. The frequency of various types of cardiac manifestations in CVID patients

Cardiac manifestations	Total (%)
Myocardial diseases	5(1.4%)
Valvular heart diseases	4(1.1%)
Pericardial diseases	6(1.7%)
Congenital heart diseases	4(1.1%)
Arrhythmia	4(1.1%)
Pulmonary hypertension	5(1.4%)
Other manifestations	9(2.6%)

Table 3. Comparison of clinical manifestations between CVID patients with and without cardiac manifestations

Type of manifestations	CVID without cardiac manifestations (n=306)	CVID with cardiac manifestations (n=31)	*P*-value
Pneumonia (%)	202(66.0%)	25(80.6%)	0.098
Otitis media (%)	141(46.0%)	22(70.9%)	*0.008**
Sinusitis (%)	143(46.7%)	20(64.5%)	0.059
Bronchiectasis (%)	82(26.8%)	11(35.5%)	0.308
Autoimmunity (%)	76(24.8%)	10(32.3%)	0.366
Allergy (%)	64(20.9%)	6(19.4%)	0.832
Meningitis (%)	11(3.6%)	0(0.0%)	0.291
Malignancy (%)	15(4.9%)	1(3.2%)	0.673
Chronic diarrhea (%)	114(37.3%)	15(48.4%)	0.224
Lymphoproliferative disorders (%)	67(21.9%)	14(45.2%)	*0.004**
Splenomegaly (%)	79(25.8%)	18(58.1%)	*<0.001**
Hepatomegaly (%)	46(15.0%)	18(58.1%)	*<0.001**
Failure to thrive (%)	63(20.6%)	12(38.7%)	*0.021**

n, number; CVID, common variable immune deficiency.

**P*-value <0.05 has been considered as statistically significant

failure and myocarditis as a group entitled myocardial diseases were reported in 5 patients. Heart failure included right ventricular dysfunction (2 of patients), left ventricular dysfunction which is defined as left ventricular ejection fraction (LVEF) which was less than 50% (3 patients) and diastolic dysfunction (2 patients).1 patient had myocarditis defined by elevation in cardiac troponin and patient symptoms. Arrhythmias in four patients included sinus tachycardia (1 patient), sinus bradycardia (2 patients) and atrioventricular (AV) block (Mobitz II) (1 patient). Four patients had valvular heart diseases: moderate aortic valve stenosis (AS) (1 patient), moderate mitral regurgitation (MR) (3 patients), moderate tricuspid regurgitation (TR) (1 patient). The study revealed that two patients out of 5 with pulmonary hypertension which is defined as systolic pulmonary artery pressure (SPAP) more than 30 mmHg (20) had severe pulmonary hypertension (SPAP more than 60 mmHg). Finally, 6 patients had pericardial diseases (acute pericarditis: 5 patients, pericardial effusion: 6 patients). In this study, among patients with documented cardiac complications, the most frequently seen cardiac manifestation was pericardial disease.

Upper and lower respiratory tract infections were the most clinical manifestations in CVID patients (**Table 3**). A significant association was detected between the cardiac diseases and presence of otitis media (*P*=0.008). The frequency of pneumonia and sinusitis was also higher in patients with cardiac manifestations, but they were not significant (*P*=0.098 and 0.059 respectively). Investigation of other manifestations showed higher rates of lymphoproliferative disorders

(*P*=0.004), splenomegaly (*P*<0.001), hepatomegaly (*P*<0.001) and failure to thrive (*P*=0.021) in patients with cardiac disorders. Moreover, autoimmunity was higher in CVID patients with a history of cardiac manifestation (*P*=0.366). In addition, the researchers compared the ages of CVID patients at the diagnosis of cardiac manifestation in all seven groups. The highest median age in the patients was related to arrhythmia (26 years) (**Figure 1**).

Immunological evaluation

The analysis showed that the difference in the median of white blood cells was significant (*P*=0.040) between the patients with cardiac manifestations and those without. The analysis in the serum levels of antibodies demonstrated that IgM and IgE had lower medians in the patients with cardiac problems compared to the patients without cardiac problems (*P* = 0.390 and 0.459 respectively). In the investigation of lymphocytes including CD3+ and CD4+ T cells, there were no significant differences in the patients with cardiac manifestations compared to the patients without cardiac problems (*P* =0.132 and 0.146, respectively). However, there were significant differences between the CD8+ T cells and CD19+ B cells in the two groups (*P* =0.020 and 0.040, respectively)

Discussion

There are few reports of cardiac disorders in patients with CVID (5). In a cross-sectional study of 30 primary immune deficient patients (including 22 CVID) which 50% had bronchiectasis; 67% of the patients had at least one abnormality in echocardiography; pulmonary hypertension was the most common finding (20). The results of the retrospective study showed that 9.1% of the patients had a history of cardiac disorder, meaning that they had been diagnosed with

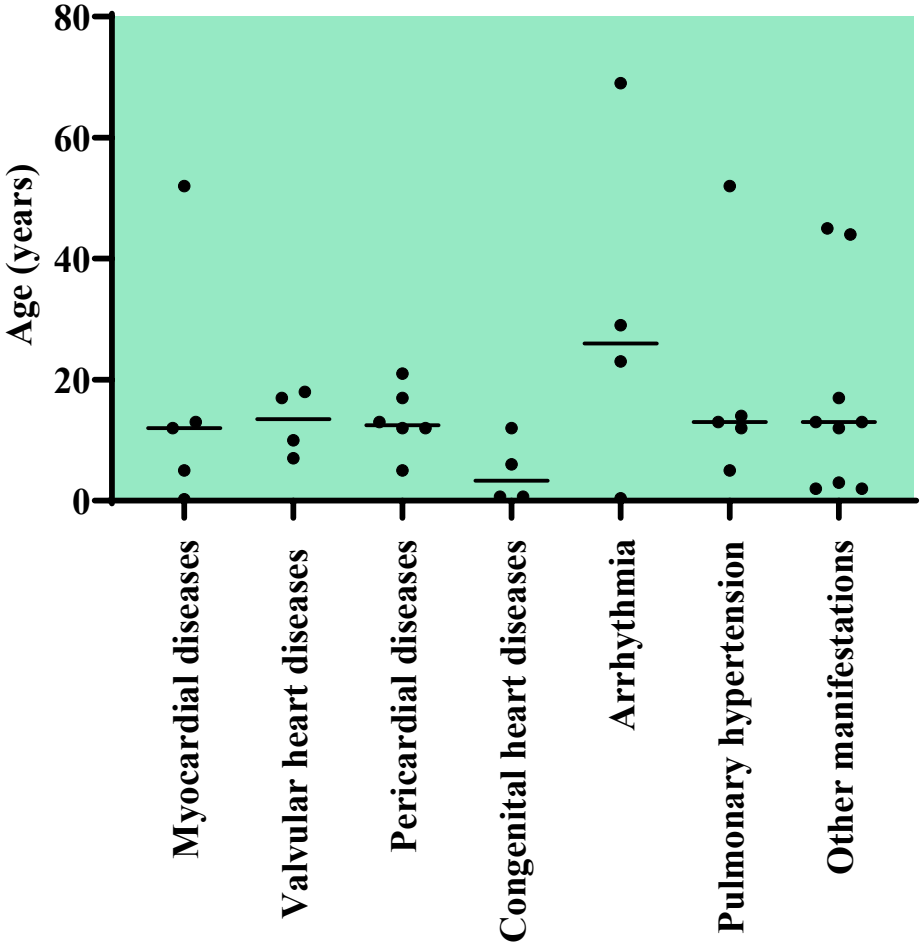

Figure 1. Age distributions and median age of CVID patients at the onset of cardiac manifestations

heart disease (6 groups) or they had a nonspecific cardiac finding that we put these patients in the group of other manifestations. Pericardial disease was the most common manifestation among patients with documented cardiac complications.

In the current study, 5 patients (1.4%) had a medical history of pulmonary hypertension in echocardiography and three of them had bronchiectasis, one of them had ASD with RV dysfunction. Pulmonary hypertension was reported in 26.5% of patients with ASD and development of pulmonary hypertension in ASD should be considered (21). In the present study, the researchers found bronchiectasis in 27.5% of the total CVID patients. A direct correlation was reported between SPAP and high-resolution computed tomography (HRCT) bronchiectasis score (20). Johnston et al. reported a cross-sectional study of 20 patients that in 45% of the patients (19 CVID patients and 1 patient with IgG2 subclass deficiency) bronchiectasis and pulmonary hypertension (mean pulmonary artery pressure more than 25 mm Hg) were found with 55% frequency (6). In their study, it was reported that despite high incidence of bronchiectasis in CVID patients, there is low incidence of pulmonary artery hypertension, but SPAP of the patients significantly had high cutoff level (22). It can be concluded that echocardiographic evaluation of CVID patients especially those with bronchiectasis for pulmonary hypertension could have an important role.

The possible association between CVID and cardiac manifestations might be due to immune dysregulation like autoimmunity. There is a case report of a patient with CVID who presented giant cell myocarditis. This manifestation is an autoimmune myocarditis (9). The researchers of the current study also found a six-years-old patient presented myocarditis at three months of age, in this patient myocarditis defined by abnormal cardiac biomarkers and patient symptoms. Due to AHA/ACCF/ESC joint scientific statement recommendation, endomyocardial biopsy (EMB) should be performed (Class I indication) in patients with heart failure and in 1) a dilated or normal sized left ventricle, <2 weeks of symptoms, and hemodynamic compromise and also in 2) patents with a dilated ventricle, 2 weeks to 3 months of symptoms, new ventricular arrhythmias or Mobitz type II or third degree heart block, or who fail to respond to regular care within 1–2 weeks (23), so because of stable hemodynamic status, EMB was not performed for the patient with myocarditis. We demonstrated that CVID patients with cardiac problems had significantly higher frequencies of otitis media, lymphoproliferative disorders, hepatomegaly, splenomegaly and failure to thrive compared to the patients without cardiac manifestations. Certain CVID manifestations, such as recurrent infections, are likely to be the result of immunodeficiency and Otitis media, like any other respiratory infection in CVID patients, is caused by immunodeficiency. However, other complications like autoimmunity and lymphoproliferation are associated with distinct immunological abnormalities and it may result from immune dysregulation rather than immunosuppression (24). It has been demonstrated that splenomegaly in CVID is common in autoimmune conditions such as interstitial lung disease and autoimmune gastrointestinal disease (25). Furthermore, the study showed that CVID patients with cardiac complications significantly had lower numbers of CD8+ T cells and CD19+ B cells. It has been shown that there is a significant decrease in naive CD4+ and CD8+ T cell repertoire, particularly in those patients with polyclonal lymphoproliferation or autoimmune cytopenias. Therefore, in this study, manifestations and cardiac findings can be the result of infectious causes, autoimmunity and immune dysregulation.

In our previous study, we reported five patients with the history of acute pericarditis. Pericardial effusion was found in all five cases, and all of them had experienced recurrent pneumonia and respiratory infections. One of these five patients had three episodes of acute pericarditis and she was not diagnosed with CVID at the first episode and she was not treated with intravenous immunoglobulin (IVIG) more than two months in the second and third episodes. Although no specific etiology for this patient's manifestations was recorded in her medical file, she had a positive blood culture for streptococcus pneumoniae during acute pericarditis which can cause infectious pericarditis in immunodeficiency (7) and it may be the reason. Autoimmunity is another reason for pericardial disease like

pericardial effusion and acute pericarditis (8, 16).

Valvular heart disease was reported in four patients' medical files. In a cross-sectional study in 26 adult patients with CVID, echocardiography showed 17 patients with mitral insufficiency, 2 patients with aortic stenosis and 24 patients had tricuspid insufficiency; it was suggested that this high incidence of valvular regurgitation was due to degenerative changes (22). But in our study, valvular heart disease was reported in patients who were younger than 25 years.

We had limitations in this study due to incomplete patient medical records. But this study could show the importance of CVID patients' follow-up in assessing cardiac problems and CVID patients with chronic pulmonary infections, congenital heart diseases and severe valvular heart diseases should be monitored for complications such as pulmonary hypertension and inflammatory heart disease.

Conclusion

Regular echocardiographic evaluation of CVID patients for cardiac complications especially for inflammatory cardiac disease and pulmonary hypertension is critical for lower risk of heart disease. Further studies are needed in patients with primary immune deficiency and CVID for possible cardiac complications.

Funding

This work was supported by the vice chancellor for research, Alborz University of Medical Sciences.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement

The authors would like to thank the Clinical Research Development Unit, Alborz University of Medical Sciences, Karaj, Iran.

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.
2. Knight AK, Cunningham-Rundles C. Inflammatory and autoimmune complications of common variable immune deficiency. Autoimmun Rev. 2006;5(2):156-9. 10.1016/j.autrev.2005.10.002.
3. Cunningham-Rundles C, Maglione PJ. Common variable immunodeficiency. J Allergy Clin Immunol. 2012;129(5):1425-6.e3.
4. Yazdani R, Habibi S, Sharifi L, Azizi G, Abolhassani H, Olbrich P, et al. Common Variable Immunodeficiency: Epidemiology, Pathogenesis, Clinical Manifestations, Diagnosis, Classification, and Management. J Investig Allergol Clin Immunol. 2020;30(1):14-34.
5. Human A, Murguia-Favela L, Benson L, Roifman I, Grunebaum E. Cardiovascular abnormalities in primary immunodeficiency diseases. Lympho Sign J. 2014;2(3):107-34.
6. Johnston SL, Hill SJ, Lock RJ, Dwight JF, Unsworth DJ, Gompels MM. Echocardiographic abnormalities in primary antibody deficiency. Postgrad Med J. 2004;80(942):214.
7. Ramzi N, Yazdani S, Talakoob H, Jamee M, Karim H, Azizi G. Acute pericarditis: A peculiar manifestation of common variable immune deficiency. Allergol Immunopathol (Madr). 2021;49(3):115-9.
8. Payandeh P, Khoshkhui M, Jabbari Azad F, Farid Hosseini R. A Patient With Common Variable Immunodeficiency and Pericardial Effusion: A Case Report and Review of Literature. J Pediatr Rev. 2019;7(3):177-80.
9. Laufs H, Nigrovic PA, Schneider LC, Oettgen H, Del NP, Moskowitz IP, et al. Giant cell myocarditis in a 12-year-old girl with common variable immunodeficiency. Mayo Clin Proc. 2002;77(1):92-6.
10. Kashef S, Moghtaderi M, Borzouee M, Rezaei N. Giant aneurysm of thoracic and proximal abdominal aorta in a patient with common variable immunodeficiency. Iran J Allergy Asthma Immunol. 2011;10(2):133-7.
11. Abolhassani H, Kiaee F, Tavakol M, Chavoshzadeh Z, Mahdaviani SA, Momen T, et al. Fourth Update on the Iranian National Registry of Primary Immunodeficiencies: Integration of Molecular Diagnosis. J Clin Immunol. 2018;38(7):816-32.
12. Diagnostic criteria of CVID: [Available from: https://esid.org/Working-Parties/Registry/Diagnosis-criteria.
13. Cooper LT, Jr. Myocarditis. N Engl J Med. 2009;360(15):1526-38.
14. Inamdar AA, Inamdar AC. Heart Failure: Diagnosis, Management and Utilization. J Clin Med. 2016;5(7):62.
15. Maganti K, Rigolin VH, Sarano ME, Bonow RO.

Valvular heart disease: diagnosis and management. Mayo Clin Proc. 2010;85(5):483-500.
16. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921-64.
17. Sun R, Liu M, Lu L, Zheng Y, Zhang P. Congenital Heart Disease: Causes, Diagnosis, Symptoms, and Treatments. Cell Biochem Biophys. 2015;72(3):857-60.
18. Fu DG. Cardiac Arrhythmias: Diagnosis, Symptoms, and Treatments. Cell Biochem Biophys. 2015;73(2):291-6.
19. Yaghi S, Novikov A, Trandafirescu T. Clinical update on pulmonary hypertension. J Investig Med. 2020;68(4):821-7.
20. Zeinaloo AA, Aghamohammadi A, Shabanian R, Salavati A, Abdollahzade S, Rezaei N, et al. Echocardiographic abnormalities and their correlation with bronchiectasis score in primary antibody deficiencies. J Cardiovas Med (MD). 2010;11(4):244-9.
21. Providência R, Botelho A, Quintal N, Costa M, Quaresma A, Lopes P, et al. Pulmonary hypertension in patients with ostium secundum atrial septal defect--is it related to echocardiographic complexity? Rev Port Cardiol. 2009;28(10):1087-96.
22. Cambray-Gutiérrez JC, Fernández-Muñoz MJ, Del Rivero-Hernández LG, López-Pérez P, Chávez-García AA, Segura-Méndez NH. Structural and functional heart diseases in adult patients with common variable immunodeficiency. Rev Alerg Mex. 2015;62(2):91-7.
23. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol. 2007;50(19):1914-31.
24. Maglione PJ. Autoimmune and Lymphoproliferative Complications of Common Variable Immunodeficiency. Curr Allergy Asthma Rep. 2016;16(3):19.
25. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Ann Allergy Asthma Immunol. 2019;123(5):454-60.