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Infectious Complications in Patients with Common Variable Immunodeficiency (CVID) in Iran

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Abstract

Background/objectives: CVID is a common primary immunodeficiency (CVID) is a common primary immunodeficiency disease that can be defined as a failure in B cell differentiation and impaired immunoglobulin production. Subsequently, the CVID patients are remarkably susceptible to recurrent and multiple infections with bacterial, viral or fungal agents. In the present study, we aimed to provide an update report on different infectious complications in the patients with CVID in Iran.

Methods: Demographic, clinical, and immunologic data as well as a history of infections with the related microbial pathogens were obtained from records of the patients diagnosed with CVID, and were followed up at Children's Medical Center. Based on the presence of meningitis, osteomyelitis, and sepsis; 2 groups of severe infections and non- severe infections were selected for further investigations.

Results: Among 301 CVID patients enrolled, 15 (5%) had severe and 286 (95%) had non-severe infections. Respiratory followed by gastrointestinal tract problems (83.1 and 71.4%, respectively) were the most common involved organs. Out of the infectious complications, lower and upper respiratory tract infection followed by mucocutaneous and gastrointestinal tract, were the most frequent ones (76.1, 64.8, 21.6, and 19.6%, respectively). *Also, Candida* followed by *Giardia lamblia* were the most common detected pathogens in those with opportunistic infections and infectious diarrhea, respectively.

Conclusions: Recurrent infections of various parts of the body are the most prevalent manifestation among the patients with CVID, which play an important role in the morbidity and even mortality in those with prolonged and untreated infections. Recurrent infections initiating early in childhood should be paid more attention, and trigger further immunological work up for a possible underlying immunodeficiency, especially in those families with consanguineous marriage and/or a positive family history of primary immunodeficiency.

Keywords: common variable immune deficiency, immunoglobulin, infectious complications, microbial agents

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Introduction

CVID is a rampant disorder defined by defective B lymphocyte differentiation, impairment in immunoglobulin production, and susceptibility to recurrent sinopulmonary infections (1). Other phenotypes of CVID are autoimmune manifestations, lymphoproliferation, and neoplastic disorders (2). Majority of CVID cases exist sporadically; however, 5-25% of these patients have a positive family history ofantibody immunodeficiency (3, 4). Although no genetic defects are specified in most of the CVID patients, studies have reported the monogenic forms of CVID in approximately 2-10% of the cases (5). These include mutations in the *ICOS*, *NFKB1*, *NFKB2*, *CD20*, *LRBA*, *STAT3*, *TACI*, and *BAFF-R* genes (3, 6, 7). Both children and adults manifest different ages of onset and disease severity (8). The incidence of CVID is estimated to be 1 per 25000-50000 live births depending on the population ethnicity (9). Since the determining factor in the given disease is the B cell dysfunction, the affected individuals are more prone to the opportunistic infections caused by various pathogens. There is a wide spectrum of clinical manifestations in the CVID patients from acute/chronic infections and autoimmunity to the increased risk of cancer (10).

The majority of the CVID patients present a wide range of infectious complications involving various parts of the body such as respiratory, gastrointestinal, and genitourinary tracts; joints; and mucocutaneous surface (11). Among the respiratory tract infections, sinusitis, otitis media, bronchitis, and pneumonia; among gastrointestinal tract infections, pathogenic chronic diarrhea, gastritis, and enteropathy; and candidiasis and fungus lesions in mucocutaneous infections are notable (12). Autoimmune manifestations occur in approximately 20% of the CVID individuals, which can affect the hematologic and vascular system, gastrointestinal tract, lungs, joints, and endocrine organs (13). The pathogenesis of autoimmunity in these subjects remains still unidentified (14).

Given the high frequency of recurrent infections and consequences of delay on diagnosis and treatment; in the present study, we aimed to provide an update report on the frequency of infectious complications of various parts of the body among the patients diagnosed with CVID in Iran.

Materials and methods

Study population

A total number of 301 subjects diagnosed with CVID were referred to the Research Centre for Immunodeficiency at the Children's Medical Centre (Pediatrics Center of Excellence affiliated to the Tehran University of Medical Sciences, Tehran, Iran). The diagnosis of CVID was performed in terms of the newest criteria proposed by the European Society of Immune Deficiencies (ESID) by considering at least one of the followings: increased susceptibili-

ty to infection, autoimmunity, granulomatous disease, unexplained polyclonal lymphoproliferation, or an affected family member with antibody deficiency, along with the marked decrease of IgG and IgA with or without low IgM, and poor antibody response to vaccines or low switched memory B cells. Also, secondary causes of hypogammaglobulinemia were excluded and there was no evidence of profound T-cell deficiency. Diagnosis of CVID was established after the 4th year of life, although the symptoms may present before this age. (15). This study was confirmed by the Ethics Committee of the Tehran University of Medical Sciences and written consent forms were obtained from the participants or from their parent(s) after informing them about the study procedures.

Data collection

According to the ethical considerations, comprehensive data on the CVID patients were collected using a 2-page questionnaire. Demographic data include gender, age, consanguinity, family history of a PID, age at the time of onset, age at the time of diagnosis, delay in diagnosis, course of the disease, and follow up periods. Also, clinical manifestations including type of infections, type of pathogens, organomegaly, autoimmunity, and other complications were assessed. Various laboratory data such as CBC, serum levels of immunoglobulins, and CD markers were collected as well. Data of the found microorganisms were obtained from the patients' medical records.

Based on the presence of 3 major infections as meningitis, osteomyelitis, and sepsis; the studied patients were divided into 2 groups of those with "severe infections" and those with "non-severe infections". The subjects with the above-mentioned infections were considered as the severely infected group while the others were classified as the non-severely infected group.

Statistical analysis

The final collected data were analyzed using SPSS software (SPSS Inc., version 24, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were also used to check data normality. Qualitative values and quantitative results were showed as frequencies with percentile and mean of ± standard deviation (SD) and median (interquartile range, IQR, presented as a range with 75th–25th percentiles), respectively. Among the statistical tests, Fisher's exact and Chi-Square were included. For comparing the numerical variables, Mann– Whitney U and Kruskal-Wallis H test were used. Central and descriptive statistics were reported for quantitative data. For the variables with skewed distribution, median and interquartile range rang (IQR) were reported as the index of data dispersion. Analytical analyses were performed using Mann-Whitney and Chi- square or Fisher's exact tests.

Results

In this study, a total of 301 CVID patients (male to female ration, 1.35:1) with an average age of 15 years old (range: 1-67 years old) were enrolled. 15 (5%) patients were severely infected and the remaining 286 (95%) individuals were non-severely infected. (**Table 1**) provides demographic data for the total CVID patients as well as the 2 classified groups and their analytical comparison. None of the demographic variables were significantly different between the 2 groups.

Upper respiratory tract infections followed by lower respiratory tract infections and diarrhea were the first and the most frequent symptoms among the studied CVID patients (25.2%, 23.9%, and 18.3%, respectively). Complete data on the first presentations of the study population is shown in **Figure 1**.

Table 2 represents detailed information on the clinical manifestations and organ involvements among the total CVID patients, the 2 classified groups, and their analytical comparison.

Table 1. Demographic data of total CVID patients, those with severe and non-severe infections and their comparison

Parameters		Total patients (n=301)	Severely infected (n=15)	Non-severely infected (n=286)	*p*-value
Sex	Male	173 (57.5)	7 (46.7)	153 (57.7)	0.399
N (%)	Female	128 (42.5)	8 (53.3)	112(42.3)	
Vital	Alive	188 (62.5)	8 (53.3)	180 (62.9)	
status	Dead	56 (18.6)	5 (33.3)	51 (17.8)	0.394
N (%)	Unknown	57 (18.9)	2 (13.3)	55 (19.2)	
Consanguinity N (%)		165 (54.8)	11 (73.3)	147 (55.5)	0.180
Positive family history for PID N (%)		33 (11)	4 (26.7)	26 (9.8)	0.240
Age of onset median (IQR), month		24 (6-84)	12 (12-24)	24 (6-84)	0.854
Age at diagnosis median (IQR), month		108 (36-230)	118.5 (67.5-180)	111 (36-240)	0.980
Delay in diagnosis median (IQR), month		48 (12-105)	94 (55-140)	48 (12-96)	0.102
Course of the disease median (IQR), month		189 (60-288)	276 (69.5-342)	192 (78-288)	0.229
Follow up period median (IQR), year		131 (12-198)	192 (8.75-233.2)	131 (24-197)	0.727

N, number; PID, primary immunodeficiency disorder, IQR, interquartile range rang.
*P-value <0.05 in considered statistically significant.

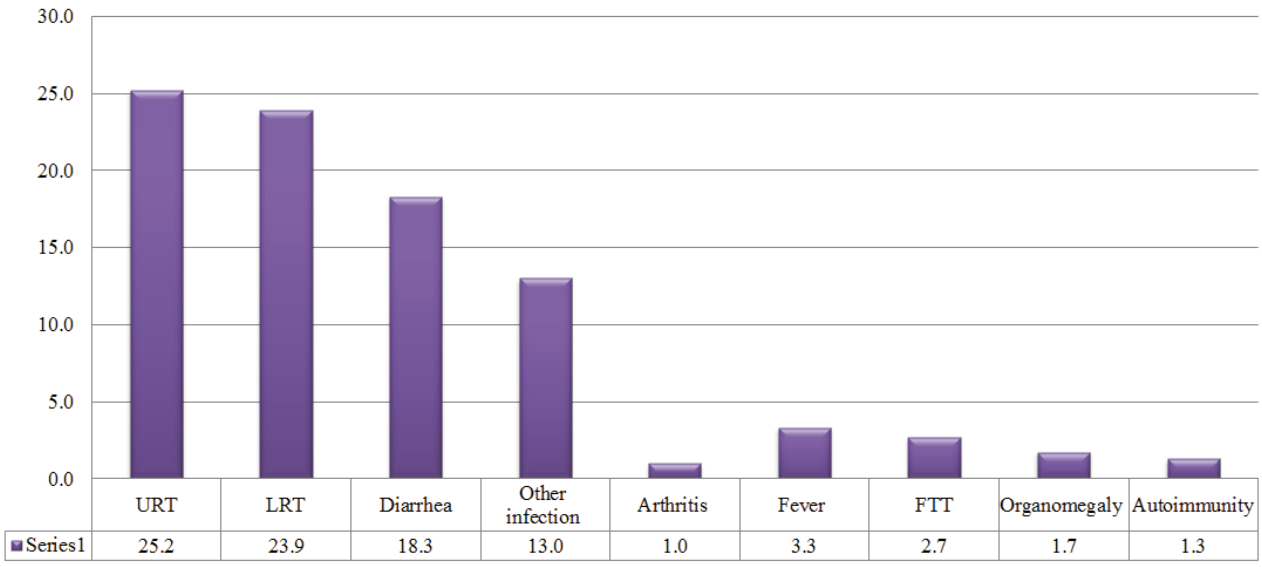

Figure 1. First presentations of the studied CVID patients
Abbreviations: URT, upper respiratory tract infection; LRT, lower respiratory tract infection; FTT, failure to thrive.

Respiratory (83.1%) followed by gastrointestinal (71.4%) tracts were the most common involved organs among the total studied CVID patients. Furthermore, 81.4% of the patients had involvement of more than one organs that can be defined as multiple sites problems. The patients with severe infection had significantly more chronic diarrhea compared to the patients with non-severe infections (73.3% versus 39.2%; P=0.009). Also, anemia was significantly more frequent in those with severe infections (40% versus 16.2%, P=0.011). Additionally, musculoskeletal and neurological problems were significantly higher in the severely infected group compared to the non-severely infected individuals (33.3% versus 6.8%, P=0.046 and 93.3% versus 20.4%, P=0.000, respectively).

Table 2. Clinical manifestations and organ involvement of total CVID patients, those with severe and non-severe infections and their comparison

Parameters, N (%)	Total patients (n=301)	Severely infected (n=15)	Non-severely infected (n=286)	*P*-value
Respiratory tract problems	250 (83.1)	15 (100)	234 (88.3)	0.160
Gastrointestinal problems	215 (71.4)	12 (80)	196 (74)	0.740
Chronic diarrhea	118 (39.2)	11 (73.3)	104 (39.2)	0.009*
Autoimmunity	81 (26.9)	7 (46.7)	71 (26.8)	0.095
Allergy	63 (20.9)	6 (40)	56 (21.1)	0.087
Malignancy	14 (4.7)	0 (0)	13 (4.9)	0.380
FTT	72 (23.9)	3 (20)	67 (25.3)	0.646
Tooth decay	10 (3.3)	1 (6.7)	9 (3.4)	0.507
Urinary tract problems	47 (15.6)	4 (26.7)	43 (16.2)	0.972
Heart problems	31 (10.3)	2 (13.3)	29 (10.9)	0.666
Hematologic problems	69 (22.9)	5 (33.3)	64 (24.2)	0.576
Anemia	49 (16.3)	6 (40)	43 (16.2)	0.011*
Neutropenia	18 (6.0)	1 (6.7)	17 (6.4)	0.598
Thrombocytopenia	26 (9)	2 (13.3)	24 (9.1)	0.890
Leukopenia	12 (4.0)	1 (6.7)	11 (4.2)	0.956
Pancytopenia	18 (6.0)	1 (6.7)	16 (6)	0.671
Lymphoproliferative	83 (27.6)	7 (46.7)	74 (27.9)	0.119
Rheumatoid problems	62.0 (20.6)	5 (33.3)	56 (21.1)	0.760
Musculoskeletal problems	23 (7.6)	5 (33.3)	18 (6.8)	0.046*
Neurologic problems	69 (22.9)	14 (93.3)	54 (20.4)	0.000*
Dermatologic problems	112 (37.2)	6 (40)	103 (38.9)	0.276
Oral ulcer	45 (15.0)	2 (13.3)	42 (15.8)	0.790
Endocrine problems	25 (8.3)	1 (6.7)	103 (38.9)	0.727
Multiple sites problems	245 (81.4)	13 (86.7)	24 (9.1)	0.621

N, number; FTT, failure to thrive.

**P*-value <0.05 in considered statistically significant

According to our findings, more than half of the patients (58.5%) had recurrent infections. Infections of the lower respiratory tract (76.1%) followed by the upper respiratory tract (64.8%) were the most common infections. Also, Pneumonia and bronchitis were considered as lower respiratory tract infections, while sinusitis and otitis media were classified as the upper respiratory tract infections. The patients with multi-infections were those with simultaneously more than one infectious episode and had a frequency of 65.4% among the total CVID patients. Also, those with severe infections had significantly higher frequency of multi- infections compared to the non-severely infected patients (100% versus 68.7%; *P*=0.007) (**Table 3**).

In microbiological view of the study, multiple bacterial, viral, and fungal agents were detected from the different infections. The most frequent pathogens were *Candida* (47 patients, 53.4%) followed by *Giardia lamblia* (14 patients, 16%) among the total CVID patients. Frequency of different detected pathogens among the studied patients are presented in details in **Figure 2**.

Detailed immunological data of the total CVID patients, the two classified groups, and their analytical comparison are shown in the **Table 4**. Among the immunological characteristics, only the absolute count of CD3 lymphocytes was significantly lower in the non-severely infected group compared to the severely infected one [median (IQR): 74 (63-82) versus 80 (76-88) cells/μL, *P*=0.013).

Table 3. Infectious complications of total CVID patients, those with severe and non-severe infections and their comparison

Parameters, N (%)	Total patients (n=301)	Severely infected (n=15)	Non-severely infected (n=286)	*P*-value
Recurrent infection	176 (58.5)	11 (73.3)	162 (61.1)	0.344
Lower respiratory tract infections	229 (76.1)	11 (73.3)	218 (82.3)	0.488
Pneumonia	207 (68.8)	11 (73.3)	196 (74)	0.957
Upper respiratory tract infections	195 (64.8)	10 (66.7)	185 (69.8)	0.778
Otitis media	149 (49.5)	11 (73.3)	137 (51.7)	0.102
Sinusitis	149 (49.5)	9 (60)	140 (52.8)	0.588
Conjunctivitis	40 (13.3)	2 (13.3)	38 (14.3)	0.914
Candidiasis	61 (20.3)	4 (26.7)	57 (21.5)	0.747
Meningitis	13 (4.3)	13 (86.7)	0 (0)	0.000*
Urinary tract infections	9 (3)	1 (6.7)	8 (3)	0.395
Mucocutaneous infection	65 (21.6)	4 (26.7)	61 (23)	0.755
Skeletal infections	1 (0.3)	1 (6.7)	0 (0)	0.54
Gastrointestinal tract infections	59 (19.6)	5 (33.3)	54 (20.4)	0.324
Multi-infections	197 (65.4)	15 (100)	182 (68.7)	0.007*
Bronchiectasis	86 (28.6)	6 (40)	80 (30.2)	0.423

N, number.
**P*-value <0.05 in considered statistically significant

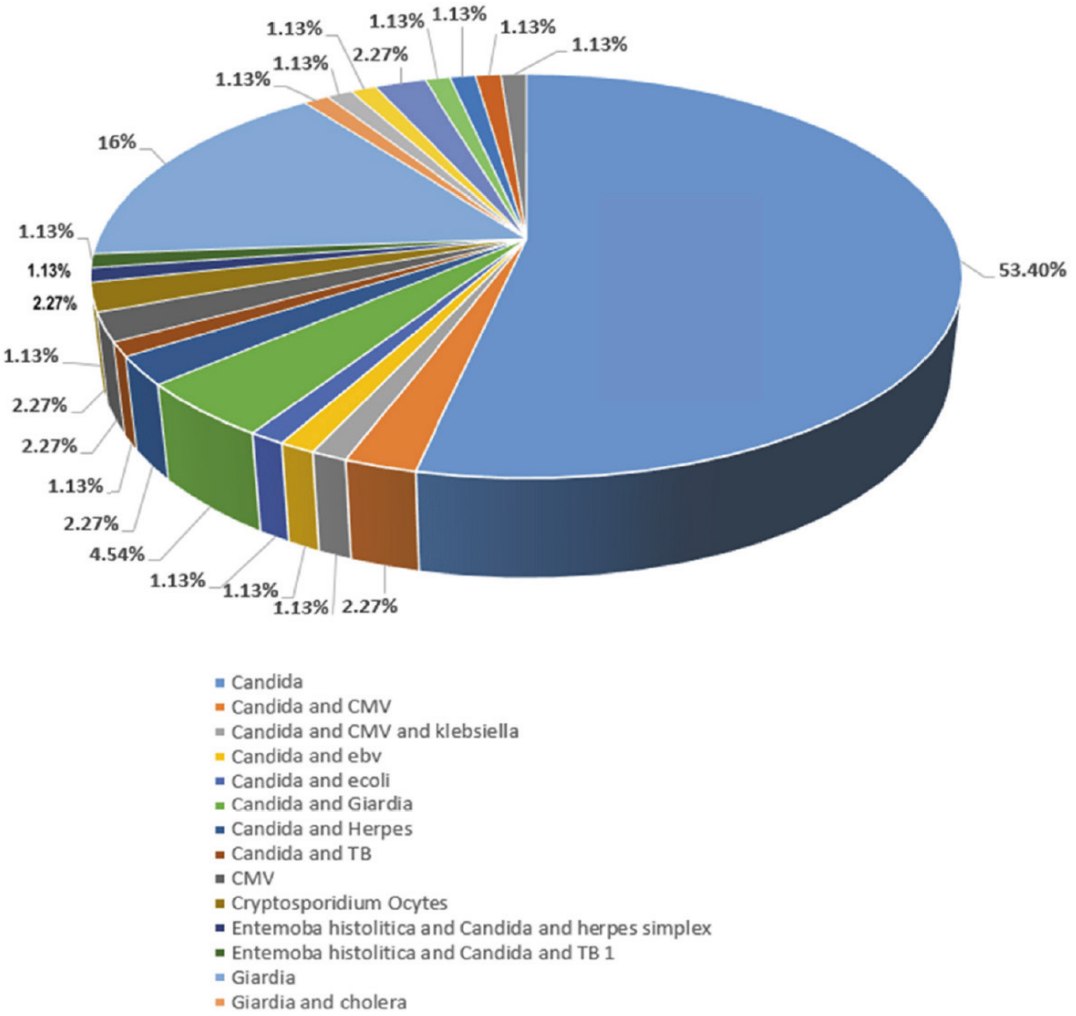

Figure 2. Frequency of various microbial pathogens detected among the studied CVID patients
Abbreviations: CMV, cytomegalovirus; EBV, Epstein Barr virus; E-coli, Escherichia coli; TB, tuberculosis

Table 4. Immunological data of total CVID patients, those with severe and non-severe infections and their comparison

Parameters	Total patients (n=301)	Severely infected (n=15)	Non-severely infected (n=286)	*P*-value
WBC count median (IQR), cells/µL	7855 (5465-10975)	8000 (5000-9500)	7855 (5667.5-11072.5)	0.364
Neutrophil count median (IQR), cells/µL	55 (41-67)	55 (40-62)	55 (42-67.2)	0.688
Lymphocyte median (IQR), %	35 (24.6-50)	40 (32-51)	34 (24-50)	0.154
Hb median (IQR), g/dl	12 (11-13)	14 (11-14.1)	12 (11-13)	0.056
Platelets median (IQR), cells/µL	231 (117-321)	214000 (305.25-293500)	230000 (121250-327250)	0.218
Absolute CD3 count median (IQR), cells/µL	74 (63.7-83)	80 (76-88)	74 (63-82)	0.013*
Absolute CD4 count median (IQR), cells/µL	32 (23-42)	34 (25.25-43.75)	32 (22.55-41)	0.430
Absolute CD8 count median (IQR), cells/µL	35 (25-50)	45.5 (29.75-57)	35 (25-49.5)	0.146
Absolute CD56 count median (IQR), cells/µL	6 (3-10)	11 (11-11)	6 (3-9.25)	0.297
Absolute CD16 count median (IQR), cells/µL	7 (5-11.5)	5 (2.925-31)	7 (5-11)	0.513
Absolute CD19 count median (IQR), cells/µL	9 (4-17)	9 (5-15.5)	9 (4-17)	0.899
Absolute CD20 count median (IQR), cells/µL	11 (4-20)	12.5 (4.5-20.5)	11 (4-19)	0.813
IgG, median (IQR), mg/dl	222 (76-470)	340 (35-500)	220 (71-470)	0.650
IgM, median (IQR), mg/dl	19 (6.7-46.2)	26.5 (15.25-110.25)	28 (13-59)	0.483
IgA, median (IQR), mg/dl	28 (13-59)	17.5 (8.5-36)	19 (6-45.5)	0.905
IgE, median (IQR), IU/ml	1 (0-5)	1 (1-26.5)	1 (0-5)	0.854

N, number; WBC; white blood cells, Hb; hemoglobin, Ig; immunoglobulins, CD; cluster of differentiation; IQR, inter-quartile range rang

**P*-value <0.05 in considered statistically significant

Discussion

Recurrent infections had the most com clinical manifestation among the CVID patients, which affected their quality of life and long - term outcome. Regarding its importance, in the present survey, we aimed to update our earlier published study and also report the newest data on the prevalence of infectious complications among the Iranian CVID patients.

In the recent years, establishment of Iranian Primary Immunodeficiency Registry (IPIDR) as well as advances in diagnostic procedures such as molecular diagnostic methods and enhancement of the physicians' knowledge on PIDs has led to earlier diagnosis and subsequently timely management of primary immunodeficient patients in the country, which itself has resulted in the increased survival rates and quality of life in these patients (16, 17). An example of that is the median of diagnostic delay in the CVID patients that has decreased from 62 months to 48 months in Iran during the last 2 decades (18).

According to previously performed stud-

ies, recurrent infections are the most prevalent clinical findings among the patients with CVID (14, 19-22). Similarly, our results were indicators of infectious complications as the leading presentations among the studied CVID patients. Defects in B cell developmental pathway in CVID is associated with hypogammaglobulinemia and impaired antibody production predisposing the patients to the recurrent bacterial infections (23). Studies have shown the effectiveness of immunoglobulin replacement therapy on decreasing the infectious episodes of upper and lower respiratory tracts, as well as invasive bacterial infections including meningitis and bacterial sepsis (12, 21, 24).

In consistent with previous reports from USA, Italy, France, and Turkey; it was indicated in our study that infections of respiratory tract (i.e. sinusitis, otitis, bronchitis, and pneumonia) were the most common infections out of the infectious complications (14, 19, 20, 22). Also, respiratory tract infections were the first and the most frequent presentations among the investigated patients of our study, which is in agreement with the results of studies by *Oksenhendler* et al. and *Quinti* et al. (14, 20). Recurrent and untreated infections of lower respiratory tract like pneumonia are shown to result in irreversible structural changes in lungs like bronchiectasis, which is associated with lower quality of life and the increased mortality (19, 25, 26). 86 of our patients (28.6%) had bronchiectasis, all of whom have been suffering from recurrent lower respiratory tract infections since early ages. Moreover, earlier diagnosis and subsequently initiation of therapy at optimal intravenous immunoglobulin G (IVIG) dosages (trough IgG target level of 5–7 g/l) are shown to decrease the number of pneumonia episodes as well as the duration of hospitalization (12, 25, 27) ; and consequently, preventing irrecoverable changes in the lungs' structure and function (22, 25).This highlights the importance of earlier detection and management of the affected patients before the occurrence of lung damage. Consequences of delay on diagnosis and treatment of these patients should be paid more attention, and the patients with respiratory symptoms, especially those with consanguine parents, with a positive family history of PID or early death in childhood, should be immunologically worked up.

Gastrointestinal tract is another common site of infections in the patients with CVID manifesting as recurrent diarrhea (28). Similar to previous studies, about one-fifth of our study population had experienced at least one episode of gastrointestinal tract infections during their disease course. Microbiological study of these patients indicated *Giardia lamblia* as the leading pathogen responsible for acute diarrhea. Other studies have also reported *G. lamblia* as the most common agent in the CVID patients with gastrointestinal infections and suggested further work-up on the affected patients for a possible underlying primary antibody deficiency (14, 20, 28- 30). Furthermore, chronic diarrhea, malabsorption, and weight loss should trigger endoscopic evaluation of the patients for other etiologies rather than infections such as autoimmune enteropathy, celiac disease, and IBD-like disease [ulcerative colitis (UC) and Crohn's disease]. So that, the affected patients could be appropriately managed and treated by steroids or immunomodulators (19, 21, 31-33).

Also, opportunistic infections have been reported in some of the CVID patients, most of whom have low number of $CD4^+$ T lymphocytes. *Haemophilus*, *Pneumocystis carinii*, *Herpes zoster*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Mycoplasma*, and *Cytomegalovirus* are some of the known organisms responsible for these infections (19-21, 34, 35). In our study, mucocutaneous candidiasis followed by cytomegalovirus enteritis were diagnosed as the opportunistic infections.

Infections of other parts of the body during CVID are possible but uncommon. These include the eyes, skin, joints, genitourinary tract, hepatitis, meningitis, and sepsis infections (14, 19, 20). This high-

lights the fact that, during CVID, almost all parts of the body are at the risk of recurrent infections with bacterial, viral, fungal, and parasital pathogens. Thus, recurrent infections in any site of the body could be suggestive of hypogammaglobulinemia as a predisposing factor, and further immunological evaluation should be made as soon as possible.

Conclusions

In the present study, we exclusively investigated the infectious complications among the patients with CVID. We demonstrated that, recurrent infections are the most common manifestations in CVID. In a descending order, the respiratory tract, mucocutaneous, opportunistic, and gastrointestinal tract infections were observed among our study population. Delay in diagnosis and treatment of these infections could lead to catastrophic complications that increase the morbidity and mortality rates among the affected patients. Further attempts should be made for the purpose of increasing the parents' awareness on PIDs, and recurrent infections of any part of the body initiating early in childhood should be considered as an alarm sign requiring further work-up, particularly in the families with consanguineous marriage or positive family history of PID, recurrent infections, and/or childhood death.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgment

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