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Original Article

Gastrointestinal Manifestations in Patients with Common Variable Immunodeficiency

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Abstract

Introduction: Common variable immunodeficiency (CVID) is one of the most prevalent symptomatic primary immunodeficiencies (PIDs), which manifest a wide clinical variability such as gastrointestinal (GI) disorder.

Methods: A total of 240 patients with CVID were enrolled in this study. The patients were evaluated for demographic data, clinical manifestations, and immunologic profile.

Results: In demographic data, the frequency of consanguinity and mortality rate were higher in patients with GI manifestation than those without GI manifestation. History of GI manifestations was evident in 147 patients (61.3%). The most common GI manifestation in patients with CVID was chronic diarrhea (29.6%). The prevalence of GI disease was 59 of 102 (57.8%) in female patients and 88 of 138 (63.8%) in male patients. The frequency of recurrent infection was higher in patients with GI manifestation than in those without GI manifestation. Also, CVID patients with GI manifestations had lower WBC and $CD4^+$ T cells than patients without GI manifestations.

Conclusions: CVID patients are at increased risk of infectious conditions in the GI tract; hence GI manifestations are one of the most important presentations in CVID patients which can appear as a first manifestation or appear during the course of disease.

Keywords Common variable immunodeficiency, Gastrointestinal manifestations, Diarrhea, Primary immunodeficiency disorder.

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Introduction

Common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency (PID) disorder characterized by hypogammaglobulinemia and increased susceptibility to recurrent bacterial infections due to (1) impaired B-cell differentiation and subsequently defective immunoglobulin production (2). The diagnosis of CVID is confirmed by laboratory investigations showing a significantly low serum IgG associated with low IgM and/or IgA, and poor or absent antibody response to vaccines (3). CVID is the most common symptomatic PID (4) which affects approximately 1 in 25,000 to 50,000 whites (5, 6). There is no gender predisposition and the age of onset is usually in the second to third decade of life, though a smaller group of patients already manifest CVID in childhood (7, 8). In general, CVID may occur at any age (8). In contrast to most other PIDs, more than 90% of documented CVID patients lack a definite molecular genetics diagnosis or other causal explanation for their disease. Only 10 to 20% of CVID patients have a positive family history, while most cases occur sporadically (7, 8). It is not a single disease, rather a clinical syndrome that represents a cluster of disorders exhibiting a common phenotype (2). A significant number of patients affected by CVID complain about gastrointestinal (GI) symptoms such as diarrhea, abdominal pain, and weight loss, though in the majority of these cases the symptoms are due to recurrent infections, particularly by Giardia Lamblia (9, 10). In addition, it has been reported that two-thirds of the patients develop different complications, including chronic inflammatory disorders (e.g. colitis, granulomas), polyclonal lymphoproliferation, autoimmune syndromes (e.g. cytopenias) and/or malignancies (e.g. leukemia, lymphoma, colon cancer) (11). Among the organ-associated disorders, GI manifestations are one of the most intractable in CVID (12). Previous studies have suggested a 9%–20% frequency of GI disease in patients with CVID (13-15) who may develop a wide range of autoimmune and autoinflammatory GI diseases (16). Importantly, the presence of GI manifestations is a major risk factor for patients with CVID, prognosing 2.7- to 4-fold increased mortality (14, 16). Acute or chronic infectious diarrhea is the most common GI symptom associated with CVID (20%–60%), leading to weight loss and malnutrition (17). Due to increased susceptibility to bacterial infection, one might assume that patients with CVID would have a higher prevalence of Helicobacter pylori (H.P) infection (12). In addition to bacterial and parasitic infections, chronic gastritis and inflammatory bowel disease (IBD) are significant problems for patients with CVID (18). The purpose of this study was to define the prevalence and type of GI manifestations in patients with CVID.

Materials and methods

Patients

The Immunodeficiency Clinic at the Children's Medical Center affiliated to Tehran University of Medical Sciences is a referral center for PID

diseases. A total of 240 patients, who were diagnosed and treated at this center between 1998 and 2018, were enrolled in this study. CVID was diagnosed based on low levels of IgG associated with low IgA and/or IgM, and poor or absent specific antibody responses, with the exclusion of other genetic or medical causes of hypogammaglobinemia (19), where IgG levels are reduced by >2 standard deviations from the mean in all patients (13). Almost all cases of CVID have reduction in IgA (usually <5 mg/dL) as well as IgM decline in about half of the cases (20, 21). Individuals with withdrawal and irregular treatment were excluded from this study. Clinical information was obtained from medical and chart records at Children's Medical Center. The process of this study was reviewed and approved by the Ethics Committee of Alborz University of Medical Sciences.

Methods

A comprehensive questionnaire was designed and the following data were collected in each case: age at clinical presentation, consanguinity, first presentation, age at diagnosis and age at last follow up, diagnostic delay, history of chronic and recurrent infections, bronchiectasis, autoimmunity, associated allergy, enteropathy, failure to thrive (FTT), lymphoproliferation, and malignancies. In each patient, laboratory data were documented, including complete blood count, white blood cell (WBC) differential and lymphocyte subsets percentage (CD3, CD4, CD8, CD19 and CD20) and serum levels of IgM, IgG, IgE, and IgA. The questionnaire was thoroughly completed for all patients at the time of diagnosis. All patients received regular immunoglobulin replacement therapy. Follow-up visits were documented every month at the time of hospital Ig administration either by interviewing the patients or reviewing patients' hospital records for occasional admissions. Diagnostic delay was defined as the time between onset of symptoms and time of diagnosis. The course of disease was measured as the duration between diagnosis and the time of either the death or last visit.

Statistical analysis

Values were presented as frequency (number and percentage), mean ± standard deviation and median (IQR), where appropriate. Fisher's exact test and chi-square tests were used for 2 × 2 comparisons of categorical variables, while t-tests and nonparametric equivalent were employed to compare numerical variables. Shapiro-Wilks test was applied to check the normality assumption for the variable; thus, according to the established assumptions, parametric or nonparametric test was conducted. Statistical analyses were performed using the SPSS software package, version 25 (SPSS Inc., Chicago, IL, USA).

Results

Baseline demographic data

In this retrospective study, after exclusion of CVID patients without complete clinical information, 240 patients [138 (57.5%) males and 102 (42.5%) females] were evaluated. The

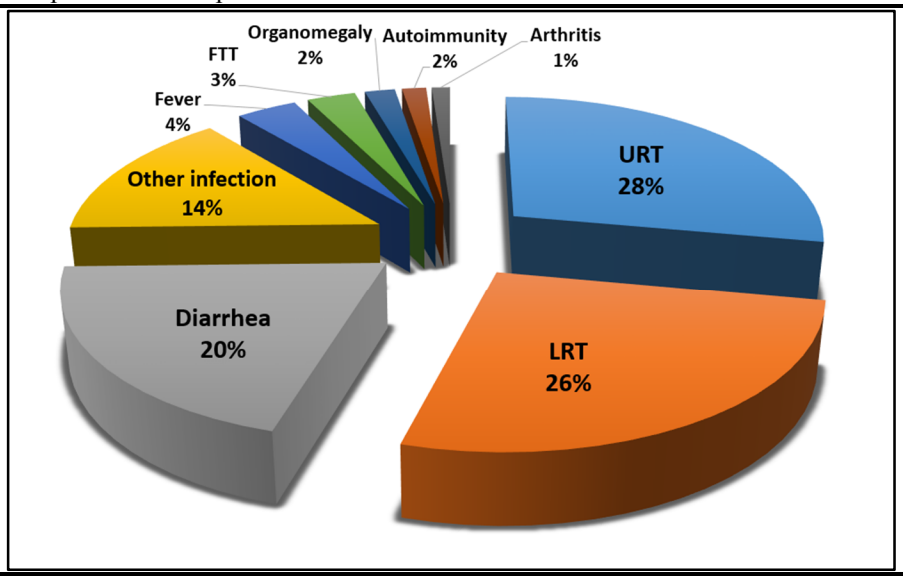
frequency of consanguinity (58.2% VS. 41.9%, P= 0.014) and dead (21.8% vs. 6.5%, p=0.007) was higher in patients with GI manifestation than those without GI manifestation. Demographic and corresponding immunologic data for the CVID are presented in **Table 1**. The most prevalent first presentation was upper respiratory tract (URT) infection (**Figure 1**).

Table 1. Demographic data of CVID patients with and without GI complications

Parameters	Total patients (n=79)	AID (n=19)	No AID (n=60)	*p*-value
Sex ratio, M/F	138/102	88/59	50/43	0.352
Family history (n=145)	26 (17.9%)	17 (18.7%)	9 (16.7%)	0.760
Consanguinity (n=239)	124 (51.9%)	85 (58.2%)	39 (41.9%)	0.014*
Dead, %	38 (15.8%)	32 (21.8%)	6 (6.5%)	0.007*
Current age, y, median (IQR), (n=187)	24.0 (14.0-32.0)	24.0 (14.0-31.0)	22.5 (11.7-33.2)	0.587
Age at onset, m, median (IQR), (n=210)	21.5 (6.0-84.0)	12.0 (5.0-66.0)	30.0 (6.0-126.0)	0.039*
Age at diagnosis, m, median (IQR), (n=215)	102.0 (25.0-228.0)	96.0 (29.0-180.0)	132.0 (24.0-270.0)	0.310
Delay in diagnosis, m, median (IQR), (n=200)	36.0 (12.0-96.0)	43.0 (12.0-108.0)	36.0 (11.0-95.5)	0.273

M; Male, F; Female, Y; Year, GI; gastrointestinal
The median is shown [with 25th and 75th percentiles].
* p-value is statistically significant <0.05.

Figure 1. The first presentation of patients with CVID



URT and LRT were the most frequent first presentation. Diarrhea as the most frequent gastrointestinal manifestations was report as the first presentation in 20% of patients. URT; upper respiratory tract, LRT; lower respiratory tract, FTT; failure to thrive

Clinical evaluation

The most prevalent clinical manifestation in patients with CVID was respiratory tract infection (81.3%). History of GI manifestations was evident in 147 patients (61.3%). The most common gastrointestinal manifestations in

patients with CVID were diarrhea (37.9%), chronic diarrhea (30.0%), and FTT (15.4%) (**Figure 2**). The most prevalent detected pathogen was *Giardia lamblia* (5.0%), *Salmonella* (0.4%), and *shigella* (0.8%). The median age of onset in patients with GI manifestation was lower than patients without this manifestation [12.0 (5.0-66.0) vs. 30.0 (6.0-126.0), p=0.039]. The prevalence of GI disease was 59 of 102 (57.8%) in female patients and 88 of 138 (63.8%) in male patients though the differences were not significant (p=0.352). Among patients with consanguineous parents, 85 patients (68.5%) had a manifestation of GI complications, while the frequency of GI manifestations in patients with non-consanguineous parents was 61 (53.0%). The frequency of recurrent infection (61.2% vs. 44.1%, p=0.009), pneumonia (71.4 vs. 58.1% p=0.033), sinusitis (53.7% vs. 32.3%,p=0.001), bronchiectasis (29.9% vs. 16.1%, p=0.016), allergy (21.8% vs. 10.8%, p=0.029), oral ulcer (18.5% vs. 3.2%, p=0.001), autoimmunity (28.6% vs. 16.1%, p=0.027), conjunctivitis (12.9% vs. 4.3%, p=0.027), and RTI (85.7% vs. 74.2%, p=0.026) was higher in patients with GI manifestation than those without GI manifestation.

Immunological evaluation

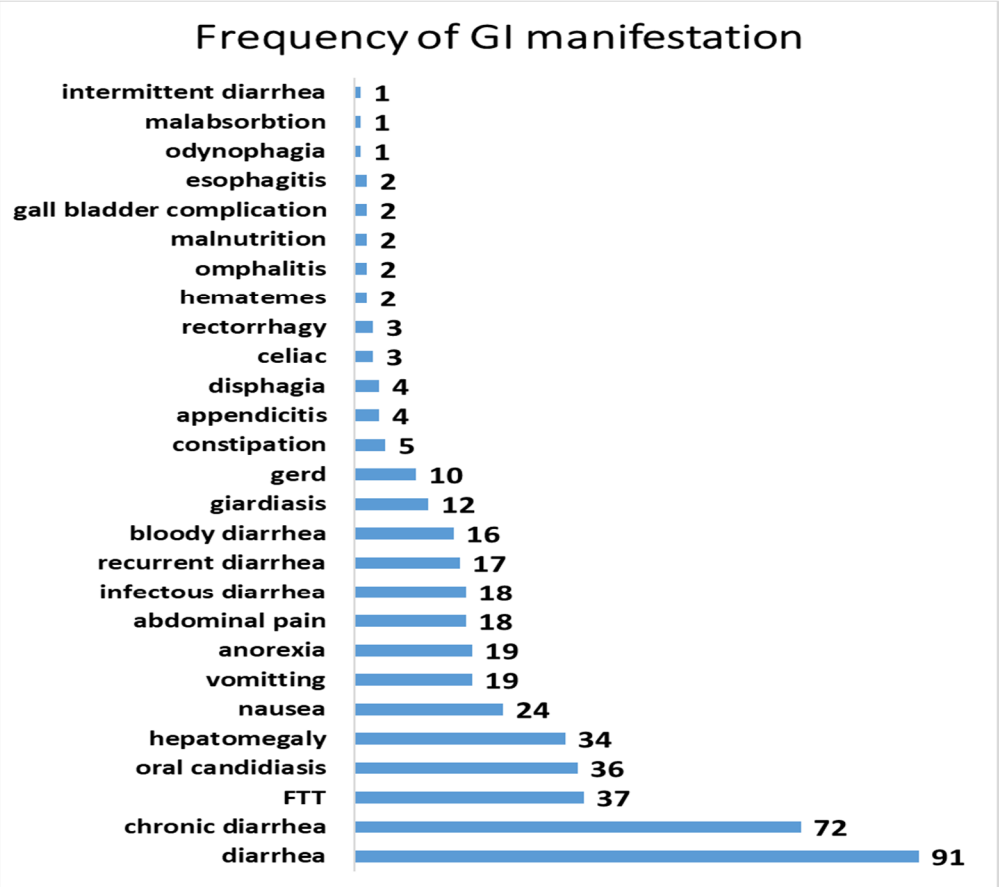
CVID patients with GI manifestations had lower WBC and $CD4^+$ T cells than patients without GI manifestations [(7300 vs. 9300, p=0.034), and (33.5 vs. 35, p=0.386)].

Table 2. Clinical manifestations of CVID patients with and without GI complications

Parameter	Total patients (n=79)	AID (n=19)	No AID (n=60)	*p*-value
Recurrent infection (%)	131 (54.6)	90 (61.2)	41 (44.1)	0.009*
Pneumonia (%)	159 (66.3)	105 (71.4)	54 (58.1)	0.033*
Sinusitis (%)	109 (45.4)	79 (53.7)	30 (32.3)	0.001*
Bronchiectasis (%)	59 (24.6)	44 (29.9)	15 (16.1)	0.016*
Otitis (%)	112 (46.7)	82 (55.8)	30 (32.3)	p<0.001*
Clubbing (%)	43 (17.9)	38 (25.9)	5 (5.4)	p<0.001*
Splenomegaly (%)	65 (27.1)	64 (43.5)	1 (1.1)	p<0.001*
Lymphoprolifrative (%)	64 (26.7)	53 (36.1)	11 (11.8)	p<0.001*
Allergy (%)	42 (17.5)	32 (21.8)	10 (10.8)	0.029*
Oral ulcer (%)	30 (12.6)	27 (18.5)	3 (3.2)	0.001*
Failure to thrive (%)	37 (15.4)	34 (23.1)	3 (3.2)	p<0.001*
Conjunctivitis (%)	23 (9.6)	19 (12.9)	4 (4.3)	0.027*
Meningitis (%)	6 (2.5)	5 (3.4)	1 (1.1)	0.409
Autoimmunity (%)	57 (23.8)	42 (28.6)	15 (16.1)	0.027*
Respiratory tract (%)	195 (81.3)	126 (85.7)	69 (74.2)	0.026*
Urinary tract (%)	30 (31.6)	21 (35.6)	9 (25.0)	0.281
Malignancy (%)	10 (4.2)	9 (6.1)	1 (1.1)	0.093

GI; gastrointestinal
* *p*-value is statistically significant <0.05

Figure 2. The frequency of GI manifestation in patients with CVID (number of patient)



GI; gastrointestinal, FTT; failure to thrive

CVID patients who had GI manifestations had a higher level of IgM, IgA, IgG [(28.5 vs. 26.5, p=0.185), (19.0 vs. 12.0, p=0.269), (258.5 vs. 160.0, P=0.097)] than patients without GI manifestations though the differences were not statistically significant.

Discussion

CVID is a heterogeneous group of antibody deficiency disorders characterized by reduced serum levels of IgG and IgA or IgM. Patients with CVID suffer from a variety of infectious and noninfectious GI diseases along with recurrent bacterial infections, especially involving the upper and lower respiratory tracts (22). In a large series of 248 CVID patients, 53 subjects (21%) had GI problems (7). In Iranian patients with CVID, 86 of 115 patients had GI infections during 30 years (23). Rodríguez-Negrete et al. (24) found a prevalence of 94% for gastrointestinal diseases in adult patients with CVID, a figure significantly higher than that published by Chapel and Shradha in 2009 and 2011, who observed a prevalence of 20% to 60% (25, 26). In another study, Abolhassani et al. found that the gastrointestinal infections were common in CVID patient, such

that the gastrointestinal tract was the second organ involved in infections in 10%–40% of the CVID cases (27). In the current study, we reported that the most common GI manifestations in patients with CVID were diarrhea (37.9%) and chronic diarrhea (29.6%). Also, Hosseini et al. reported that the major GI manifestations of CVID were transient or persistent diarrhea, reported in 21-57% of subjects (28). Accordingly, gastrointestinal tract infections are common in CVID, leading to recurrent or chronic diarrhea (29). Some patients may present with GI problems as their first clinical presentation, while others develop GI complications during the course of the disease (30). Patients often present with a history of transient or persistent diarrhea, which is consistent with our results. In this present study, 20% of patients showed diarrhea as the first presentation of the immunodeficiency disease. Gastrointestinal manifestations that occur in about 10% to 20% of patients with CVID (31), may be the initial or sole presentation. Thus, gastrointestinal manifestations are one of the most important initial presentations in CVID.

Two-thirds of patients with CVID develop different complications, including chronic inflammatory disorders (e.g. colitis, granulomas), polyclonal lymphoproliferation, and autoimmune syndromes (e.g. cytopenias) (13, 32). The association between CVID and autoimmune diseases is well recognized, since autoimmune diseases occur in approximately 20–30% of patients with CVID (33). In the current study, the frequency of lymphoproliferative disorder and autoimmunity was higher in patients with GI manifestation than those without GI manifestation. These results are consistent with previous studies by Gathmann et al. and Boileau et al. who reported occurrence of autoimmunity in approximately 25% to 30% of the patients with CVID (34, 35). Also in another study, Quinti et al. described autoimmunity as one of the presenting manifestations of CVID in 17% of 224 patients (36) Similarly, Agarwal et al. reported this value as 2.3% and described autoimmune GI disease as one of the clinical complications at the time of diagnosis of CVID (18).

It is well known that CVID is characterized by a high mortality rate (37). In the current study, the mortality rate was significantly higher in patients with GI manifestation than those without GI manifestation. Previous studies reported that the age of onset is usually in the second to third decade of life, although a smaller group of patients already manifest CVID in childhood (7, 8). In a recent large (2212 patients) study from Europe, a large proportion (34%) of the patients had disease onset before age 10 years (34). However, in a European cohort of 413 patients, the age of onset was found to be a continuous curve, with a mean age of 35.3 years and median of 33 years (13). In the current study, the median age of onset in patients with GI manifestation was lower than in patients without this manifestation and in total the patients' age of onset was 21.5 (6.0-84.0). There may be significant delay between the onset of symptoms and the establishment of the diagnosis of CVID. In an

American cohort, this delay was approximately 5 to 6 years (7). In an older report of a European cohort, there was a mean diagnostic delay of 7.5 years (13) and 8.9 years in an Italian cohort (36). On the other hand, in this current study, the median age of delay in diagnosis in patients with CVID was 36.0 (12.0-96.0).

Among pathogens causing diarrhea in immunodeficient patients, the *Giardia lamblia* is one of the leading bacteria. Eren et al. found that GI infections related to *Giardia lamblia* are more observed in PID patients (38). Also, Pikkarainen et al. found 6 parasitic infections caused by *Giardia lamblia* in patients with CVID (4). In another study, Oksenhendler E et al. reported *Giardia lamblia* was the most common GI pathogen in 252 CVID patients (8). In the current study, the most prevalent detected pathogen was *Giardia lamblia* (5.0%).

CVID is characterized by reduced serum levels of IgG, IgA, and/or IgM, with diminished antibody production; because of low antibody levels, most patients have recurrent infections (33) Here, we found that the frequency of recurrent infection was higher in patients with GI manifestation than those without GI manifestation. The main immunological defect in CVID is reported to be the failure of B-cell Ig production, though abnormalities have been described in all other components of the immune system (39, 40). In a study by Rishad Khan et al., flowcytometry data were available for 47 (49%) patients with GI symptoms and 28 (29%) patients without GI symptoms for a total of 75 (79%) patients. There were no significant differences between patients with GI symptoms and those without them regarding absolute lymphocytes, CD3+ cells, CD4+ cells, CD8+ cells, and CD19+ cells (41). In the current study, we observed that CVID patients with GI manifestations had lower WBC and CD4+ T cells than patients without GI manifestations; however, most of immunologic data differences in this current study were not statistically significant. In line with these studies, in a study by Resnick ES et al. reported Of the 411 subjects with known follow-up, 93 patients (19.6%) in this US cohort followed over 4 decades had died and Kaplan-Meier survival curves also confirmed these observations, showing significantly reduced survival for patients with gastrointestinal disease (P=0.005) (15). Importantly, the presence of GI manifestations is a major risk factor for patients with CVID, prognosing a 2.7- to 4-fold increased mortality (13, 14).

Conflicts of interest: The authors declare that they have no conflicts of interest.

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