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Original Article

Gastrointestinal Disease in Patients with Common Variable Immunodeficiency: A Retrospective Observational Study

Rishad Khan, BSc[1],[○]**, Mohamad Habbal, MD[1], Michael A. Scaffidi, MEd[1],**[○]**, Abbas A. Bukhari, BSc[1],**
Amir Rumman, MD, FRCPC[1], Sarah Al Ghamdi, MD, FRCPC[1], Stephen D. Betschel, MD, FRCPC[2,*],
Samir C. Grover, MD, MEd, FRCPC[1,*]

[1]Division of Gastroenterology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [2]Division of Allergy and Clinical Immunology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

Correspondence: Samir C. Grover, MD, MEd, FRCPC Division of Gastroenterology, Department of Medicine, St. Michael's Hospital, University of Toronto, 16–036 Cardinal Carter Wing, 30 Bond Street Toronto, Ontario M5B 1W8, Canada, e-mail: samir.grover@utoronto.ca

*These two senior authors contributed equally.

Abstract

Background: Gastrointestinal (GI) symptoms are common among patients with common variable immunodeficiency disorder (CVID) yet remain poorly understood.

Aims: The aim of this study was to characterize the demographic, clinical, endoscopic and histologic features of patients with CVID and GI symptoms.

Methods: We conducted a retrospective observational study of all patients with CVID at a large Canadian tertiary care centre between January 2000 and May 2018.

Results: We included 95 patients with CVID. The mean age of patients at the time of CVID diagnosis was 38.2($\pm$16.0). Fifty-three (56%) patients were female. Sixty-four (67%) patients had GI symptoms, with a mean age of onset for GI symptoms of 43.4($\pm$15.1) years. The most common symptoms were bowel movement changes ($n = 55$ [58%]) and abdominal pain ($n = 44$ [46%]). Patients with GI symptoms were more likely to have anemia ($n = 23$ [36%] versus $n = 3$ [10%], $P = 0.0129$), iron deficiency ($n = 16$ [25%] versus $n = 2$ [7%], $P = 0.0481$), and have received GI antibiotics ($n = 37$ [58%] versus $n = 0$, $P < 0.0001$) and proton pump inhibitors for reflux ($n = 24$ [38%] versus $n = 3$ [10%], $P = 0.0067$). The most common GI infections were *Giardia lamblia* ($n = 14$ [15%]) and *Clostridium difficile* ($n = 4$ [4%]). Forty-three (45%) patients with GI symptoms underwent colonoscopy, esophagogastroduodenoscopy or both. The most common findings were inflammation, nodular lymphoid hyperplasia, reduced plasma cells and increased intraepithelial lymphocytes.

Conclusions: This is the largest study on CVID patients in a North American setting. The majority of patients experienced GI symptoms. Future studies should study response to treatment for GI disease among patients with CVID.

Keywords: *Colitis; Common variable immunodeficiency; Enteropathy*

Common variable immunodeficiency disorder (CVID) represents a collection of primary immunodeficiency phenotypes, characterized by impaired B cell differentiation and defective immunoglobulin production. While reduced B cell function and hypogammaglobulinemia are the hallmarks, deficiencies in all other immune system components have been described (1–4). The clinical presentation of CVID is heterogeneous. Patients most commonly present with recurrent sinopulmonary

bacterial infections, chronic lung disease, hematologic or organ-specific autoimmune disease, granulomatous disease and lymphoproliferative disorders (3,5–8). Many patients with CVID may also encounter various infectious and noninfectious, inflammatory diseases of the gastrointestinal (GI) tract (9–13). There is substantial variation in the description of GI pathology among patients with CVID (3,5,7,12). Diarrhoea has been the most commonly reported symptom, ranging from 20 to 60% of cases (3,8,14,15). Common GI infections in CVID patients include *Giardia, Salmonella, Campylobacter* and cytomegalovirus (CMV) (16,17). Noninfectious GI pathologies in patients with CVID include microscopic colitis, coeliac disease, lymphocytic gastritis, granulomatous disease, pernicious anemia, acute graft versus host disease, inflammatory bowel disease (IBD), CVID-enteropathy and small-bowel lymphoma (3,15,17,18). The frequency, demographic and clinical associations of these GI manifestations among CVID patients remain poorly described. Thus far, studies assessing GI tract pathology in this patient population have not reported a comprehensive data set which includes demographic, clinical, endoscopic and histopathologic features. To address these gaps, we studied GI disease in patients with CVID from a large Canadian sample.

MATERIALS AND METHODS

We aimed to quantify and characterize the demographic, clinical, endoscopic and histopathologic features of GI disease among patients with CVID. This study received approval from the Institutional Review Board at St. Michael's Hospital (17 to 200).

We identified patients followed for CVID at the immunology clinic of a large, tertiary care academic centre in Toronto, Canada. We searched for these patients' electronic medical records on Cerner Soarian Clinicals (Cerner Corporation, North Kansas City, MO). We collected data from patient records between January 2000 and May 2018. The inclusion criteria were:

1. Age ≥ 18 years
2. An established diagnosis of CVID, defined according to an international consensus statement (2): i) Age ≥ 4 years; ii) decreased serum IgG levels for adults, usually with levels of serum IgA below the lower limit of normal for age; iii) the absence of significant antibody responses to protein antigens following immunization or exposure to antigens; and iv) exclusion of other known causes of immunoglobulin deficiency.

Data collection
For each patient, we collected gender, age of CVID diagnosis and age of onset of GI symptoms. We collected data on conditions associated with CVID, including organ-specific and

hematologic autoimmune conditions, chronic lung disease, liver disease, lymphoproliferative disease and history of infections.

We also collected the following clinical data at the time of onset of GI symptoms: presence of abdominal pain, bowel movement changes, weight loss, nausea/vomiting, and bloating, history of GI disease such as IBD or coeliac disease, treatments offered for GI symptoms, and GI infections. These data were collected through review of patients' medical records and extraction of data from clinical gastroenterology notes.

Finally, we collected endoscopic, histopathologic and laboratory data, including immunoglobulin trough levels, at the date nearest to the onset of GI symptoms, within 3 months. These data were extracted if they were available in patients' records due to clinical testing over the course of their disease.

Bias
Sources of bias in this observational study include recall bias and potential confounding due to factors not assessed. Additionally, there is a risk of misclassification bias if patients in our study had GI disease that was assessed at another institution, or outside our study timeline. We sought to address these biases through systematically evaluating clinical notes and utilizing two authors (RK and MH) to independently assess all patient records. A third author resolved any disagreements (SCG).

Study Size
There was no formal sample size calculation for this study, as we included all adult patients who had a diagnosis of CVID and were followed by the immunology clinic at our institution.

Statistical Analysis
We conducted all statistical analyses using SPSS 20 (IBM, Armonk, NY). We used descriptive statistics to characterize patients with CVID; mean ± standard deviation for continuous variables, and count with percentage for categorical variables. We compared patients with and without GI symptoms to assess if there were any differences in demographic, clinical, and immunological characteristics. We used nonparametric tests (Mann–Whitney U and Kruskal–Wallis) for continuous variables (age, immunoglobulin trough levels and lymphocyte levels) and Fischer's exact test for categorical variables (gender, presence of clinical comorbidities such as anemia).

RESULTS

We included a total of 95 patients with CVID (Table 1). The mean age of CVID diagnosis was 38.2 (±16.0) years. Fifty-three (55.8%) patients were female.

Clinical, endoscopic and histopathologic findings
Sixty-four (67%) patients had GI symptoms, with a mean age of onset for GI symptoms of 43.4 (±15.1) years. Fifty-five (58%)

Table 1. Patient characteristics

Characteristic n (%) unless otherwise stated	Total (n = 95)
Demographic	
Age of CVID diagnosis, years (mean, SD)	38.2 (16)
Female	53 (56)
Clinical	
Chronic lung disease	25 (26)
Organ-specific autoimmunity	4 (4)
Autoimmune cytopenia	9 (9)
Liver disease*	7 (7)
Granulomatous disease	3 (3)
Lymphoid malignancy	2 (2)
History of Crohn's disease	3 (3)
History of microscopic colitis	5 (5)
Family history of IBD	2 (2)
Medication use	
NSAID use	21 (22)
Proton pump inhibitor use	27 (28)
Antibiotic exposure†	37 (39)
IVIG replacement	58 (61)
SCIG replacement	37 (39)
Symptomology	
Abdominal pain	44 (46)
Change in bowel movements	55 (58)
Weight loss	28 (30)
Reflux	18 (19)
Nausea/vomiting	15 (16)
Bloating	21 (22)
Microbiology	
Campylobacter	1 (1)
Clostridium difficile	4 (4)
Cytomegalovirus	3 (3)
Giardia lamblia	14 (15)
Salmonella	1 (1)

*Two patients had hepatitis B, and five patients had hepatitis C.

†Defined as at least one course of antibiotics for treatment of presumed gastrointestinal infection within 3 months of symptom onset.

CVID, Common variable immunodeficiency; IBD, Inflammatory bowel disease; IVIG, Intravenous immunoglobulin; NSAID, Nonsteroidal anti-inflammatory drug; SCIG, Subcutaneous immunoglobulin; SD, Standard deviation.

patients had bowel movement changes, 44 (46%) had abdominal pain, 28 (30%) had weight loss, 21 (22%) had bloating, 18 (19%) had reflux and 15 (16%) had nausea and/or vomiting.

Twenty-three (24%) patients underwent colonoscopy and esophagogastroduodenoscopy (EGD), 12 (13%) underwent colonoscopy only, 8 (8%) underwent EGD only and 21 (22%) did not undergo either procedure. All patients who underwent endoscopic assessment had GI symptoms. Endoscopic and

Table 2. Endoscopic and histologic findings among patients who underwent colonoscopy

Characteristic n (%), from colonic biopsies unless otherwise specified	Underwent colonoscopy n = 35
Endoscopic findings	
Normal	10 (29)
Erythema*	14 (40)
Micronodular pattern	13 (37)
Ulceration	3 (9)
Polyps	10 (29)
Diverticula	3 (9)
Histology	
Normal	7 (20)
Reduced plasma cells	6 (17)
Increased intraepithelial lymphocytes	4 (11)
Terminal ileum villous atrophy	2 (6)
Microscopic Inflammation	
Acute/indeterminate inflammation†	6 (17)
Microscopic colitis	1 (3)
Crohn's disease	1 (3)
Polyps	
Tubular adenoma	8 (23)
Tubulovillous adenoma	1 (3)
Sessile serrated adenoma	2 (6)

*Erythema was found 11 times in the colon, and 3 times in the terminal ileum.

†Acute/indeterminate inflammation was found 5 times from colonic biopsies, and once from terminal ileum biopsies.

histopathologic findings are described in Tables 2 and 3 for colonoscopy and EGD, respectively.

Twenty-three (24%) patients had GI symptoms prior to their diagnosis of CVID. For 15 (16%) patients, GI symptoms led to a diagnosis of CVID through examination of biopsies and subsequent immunological workup. For the remaining eight (8%) patients, there was a range of 4 to 10 years between the onset of GI symptoms and a CVID diagnosis. Among the latter patients, six (6%) had no endoscopic or histopathologic findings, one (1%) had microscopic colitis and one (1%) had increased intraepithelial lymphocytes.

GI infections

A total of 23 (24%) patients had GI infections, with the most common identified pathogen being *Giardia lamblia*. These were diagnosed with stool microscopy or immunoassay for *G lamblia,* stool toxin for *Clostridium difficile,* stool culture for *Salmonella* and *Campylobacter jejuni*, and serum serology with colonic biopsy for CMV. Sixteen patients (17%) received antibiotic therapy for non-*C difficile* infections, while three received antiviral therapy for CMV infection. An additional 21 (22%) patients received

antibiotics for presumed a GI infection despite no documented infectious agent. Among them, two (2%) later developed *C difficile* infections which were treated with a second course of antibiotics. The other cases of *C difficile* infection occurred following antibiotic treatment for sinopulmonary infections.

Table 3. Endoscopic and histologic findings among patients who underwent esophagogastroduodenoscopy

Characteristic n (%)	Underwent EGD n = 31
Endoscopic findings	
Normal	9 (29)
Erythema	13 (42)
Ulceration	3 (10)
Oesophageal plaques	1 (3)
Histology	
Normal	8 (26)
Reduced plasma cells	8 (26)
Increased intraepithelial lymphocytes	5 (16)
Duodenal villous atrophy	3 (10)
Reactive gastropathy	6 (19)
Intestinal metaplasia	4 (13)
Microscopic Inflammation	
Acute/chronic gastritis	10 (32)
Acute duodenitis	3 (10)

EGD, Esophagogastroduodenoscopy.

Features of those with GI symptoms versus those without GI symptoms

A comparison of patients with and without GI symptoms is provided in Table 4. The mean ages of CVID diagnosis were 37.1 (±16.6) years and 40.7 (±15.1) for patients with and without GI symptoms, respectively. Patients with GI symptoms were more likely to have anemia and iron deficiency. Patients with GI symptoms were more likely to have received antibiotics for a presumed GI infection within 3 months of onset of symptoms, and proton pump inhibitors for reflux. Patients without GI symptoms were more likely to have had chronic lung disease and autoimmune cytopenia.

All patients had serum immunoglobulin trough levels available and were on immunoglobulin replacement therapy at the time trough levels were assessed. There were no significant differences between patients with GI symptoms (n = 64 [67%]) and those without (n = 31 [33%]) (Figure 1). Patients with GI symptoms had mean IgG trough levels of 886 ± 417 mg/dL, IgA levels of 12 ± 23 mg/dL, and IgM levels of 37 ± 76 mg/dL, compared with IgG trough levels of 904 ± 283 mg/dL, IgA levels of 22 ± 38 mg/dL), and IgM levels of 136 ± 578 mg/dL among patients with no GI symptoms.

Flow cytometry data were available for 47 (49%) patients with GI symptoms and 28 (29%) patients without GI symptoms for a total of 75 (79%) patients (Figure 2). There were no significant differences between patients with GI symptoms and those without with respect to absolute lymphocytes, CD3+ cells, CD4+ cells, CD8+ cells and CD19+ cells. Data on B cell

Table 4. Difference in characteristics between patients with and without gastrointestinal symptoms

Characteristic n (%) unless otherwise stated	No gastrointestinal symptoms n = 31	Gastrointestinal symptoms n = 64	P value
Demographic			
Age of CVID diagnosis, years (SD)	40.7 (15.1)	37.1 (16.6)	0.7949
Female	17 (55)	36 (56)	0.9999
Clinical			
Anemia	3 (10)	23 (36)	0.0129
Iron deficiency	2 (7)	16 (25)	0.0481
Chronic lung disease	17 (54)	8 (13)	<0.0001
Organ-specific autoimmunity	3 (10)	1 (2)	0.1002
Autoimmune cytopenia	6 (19)	3 (5)	0.0310
Liver disease	2 (6)	5 (7)	0.9999
Granulomatous disease	1 (3)	2 (3)	0.9999
Lymphoid malignancy	1 (3)	1 (2)	0.9999
Medication exposure			
NSAIDs	5 (16)	16 (25)	0.4324
Antibiotics*	0	37 (58)	<0.0001
Proton pump inhibitor	3 (10)	24 (38)	0.0067

CVID, Common variable immunodeficiency; NSAID, Nonsteroidal anti-inflammatory drug; SD, Standard deviation.

*Defined as at least one course of antibiotics for treatment of presumed gastrointestinal infection within 3 months of symptom onset.
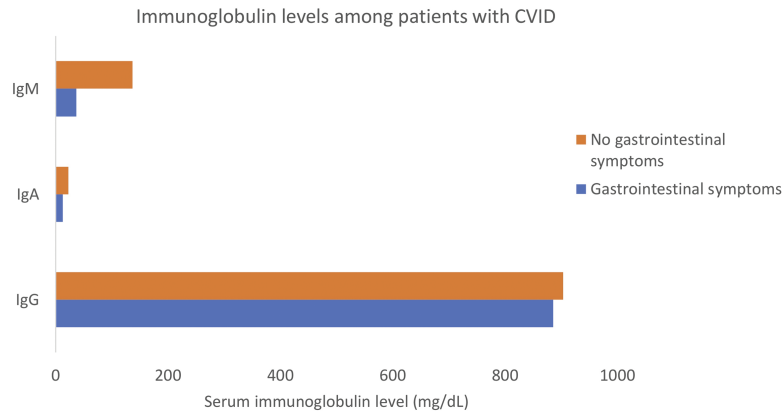
Figure 1. IgG trough levels, IgA and IgM levels are presented in mg/dL. There were no significant differences when comparing patients with gastrointestinal symptoms to those without.
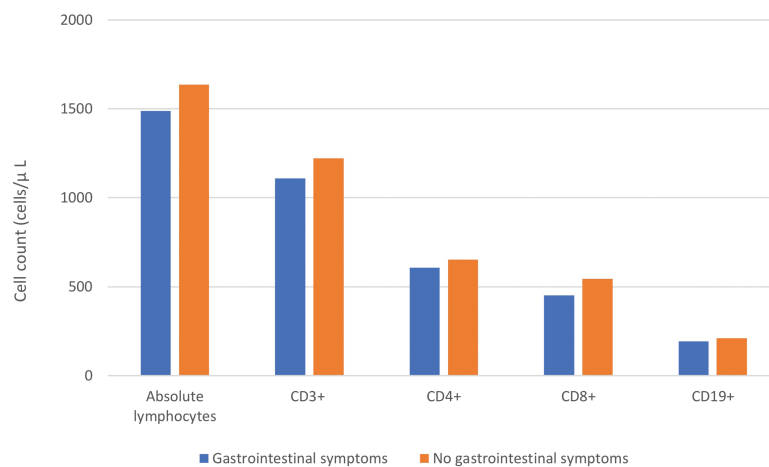

Figure 2. Flow cytometry analysis for absolute lymphocyte, CD3+, CD4+, CD8+ and CD19+ cell counts. There were no significant differences when comparing patients with gastrointestinal symptoms to those without.

phenotype (i.e., switched memory B cells, marginal zone B cells, transitional B cells) were not available as this extended immunophenotyping was not done.

DISCUSSION

We identified 95 patients with CVID at our tertiary care centre, the majority of whom experienced GI symptoms over the study period. The most common GI symptoms included change in bowel movements and abdominal pain. For several patients, GI symptoms led to a workup and diagnosis of CVID. Among the 35 patients who underwent colonoscopy, erythema and a micronodular pattern were the most common endoscopic findings, and acute/indeterminate inflammation and reduced plasma cells were the most common histologic findings. Among the 31 patients who underwent EGD, the most common endoscopic finding was gastric erythema, and the most common histologic findings were acute/chronic gastritis and reduced plasma cells. Patients with GI symptoms were more likely to

have anemia, iron deficiency, and be exposed to GI antibiotics and proton pump inhibitors. Patients without GI symptoms were more likely to have chronic lung disease. There were no differences with respect to immunoglobulin levels or T-cell levels between patients with GI symptoms and those without. The polyp detection rate in the CVID cohort was 29%, similar to that of the population screened at a similar median age ([19]).

In our study, *G lamblia* was the most common GI pathogen, consistent with a previous European study assessing infections in 252 CVID patients ([16]). *C difficile* infection was low in both our population and in the European study, with incidences of 4% and 2%, respectively. Despite their greater exposure to antibiotics, it has been postulated that CVID patients do not appear to have a higher incidence of *C difficile* infection due to the presence of anti-*C difficile* antibodies in replacement immunoglobulin products ([9,20]). Conversely, GI symptoms mimicking bacterial and subsequent antibiotic therapy may increase risk of *C difficile* colitis. Indeed, two of three cases of *C difficile* infection followed treatment for a presumed GI infection despite no

documented pathogen. Interestingly, no patients were tested for Norovirus. While this pathogen was described recently in a small case series of eight patients with CVID (21), a larger cross-sectional study did not find Norovirus to be especially prevalent (12). In our centre, a relative lack of awareness among endoscopists of the role of this infectious agent may have led to the lack of testing.

Several patients in our study had increased IELs and duodenal villous atrophy, histologic findings similar to those found in coeliac sprue (CS). We found several histologic characteristics which are absent in CS however, such as a paucity of intestinal plasma cells and lymphoid hyperplasia. These findings highlight the distinction between CVID-enteropathy and CS. A recent cross-sectional study suggested that CVID patients with 'coeliac' like disease have little or no overlap with CS patients on microarray analyses and HLA typing (12), while another study found that few patients with CVID and villous atrophy improve symptomatically with a gluten free diet (13). Several studies have also found that IBD-like disease occurs with increased frequency in patients with CVID with an estimated incidence of 6 to 10% (1,11). In our population, 3.2% of the patients had a known history of Crohn's disease and an additional patient who underwent colonoscopy was found to have active signs of Crohn's disease on biopsy. Importantly, it has been postulated that the CVID-associated colitis is distinct from classic IBD (22), with features more similar to lymphocytic colitis (23) and collagenous colitis (24). The heterogeneity in the appearance of CVID-associated colitis explains our finding that the majority of microscopic colonic inflammation found on biopsy was acute/indeterminate colitis. As such, the mechanisms of CVID-associated enteropathy, as well as colitis remain poorly understood and are likely different from classic CS and IBD.

There are several limitations of our study. First, we were unable to fully characterize response to treatment as we depended on information retrieved retrospectively from clinical records. Second, we were not able to control for variations in timing with respect to laboratory, endoscopic, and histopathologic data and their relation to the onset of GI symptoms. We did, however, maintain a degree of homogeneity by limiting the collection of these data to within 3 months of symptom onset. Finally, we did not have any endoscopic or histopathologic data from patients without GI symptoms, as they did not undergo endoscopy. Thus, we are unable to assess whether some patients may have had endoscopic or histopathologic findings in the absence of symptoms.

CONCLUSION

In this large North American study, we found that GI symptoms occurred frequently among patients with CVID, with the most common symptoms being change in bowel movements

and abdominal pain. Additionally, these patients had infectious, endoscopic and histologic findings that were comparable to previous European studies. Our study also supports the assertion that CVID-associated enteropathy and colitis are common and likely distinct from classic CS and IBD. Gastroenterologists have an important role in the care of patients with CVID, as GI symptoms are common and can often precede an immunologic workup and diagnosis. Future studies should compare response to treatment for GI disease among patients with CVID versus those without. Additionally, future studies can prospectively assess the impact of factors such as B cell phenotype on GI symptoms.

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