Primary Hypogammaglobulinaemia with Inflammatory Bowel Disease-Like Features: An ECCO CONFER Multicentre Case Series

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Primary hypogammaglobulinemia with IBD-like features: An ECCO CONFER Multicenter Case Series

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Abstract

BACKGROUND

The most commonly recognized clinical feature of hypogammaglobulinemia is recurrent infections with high prevalence of gastrointestinal manifestations. In some cases, clinical and endoscopic features are indistinguishable from those of inflammatory bowel disease (IBD).

METHODS

This was a multicenter case series performed as a part of the Collaborative Network of Exceptionally Rare case reports (CONFER) project.

RESULTS

This report includes 27 patients with primary hypogammaglobinemia and IBD-like features [20 males and 7 females, median age 45.6 years (Interquartile range (IQR) 35.2-59]. Crohn's disease-like features were noted in 23 patients, four patients had ulcerative colitis-like features. The diagnosis of hypogammaglobulinemia preceded IBD-like features diagnosis in 20 patients (median of 7 years prior, IQR 2.6-20.6years), and followed IBD-like features appearance in 7 cases (median of one year after, IQR 0.45-5.6 years).

Hypogammaglobinemia etiologies were common variable immunodeficiency (66.6%), agammaglobulinemia (7.4%), selective IgA-deficiency (11.1%), Goods syndrome (7.4%), IgG subclass deficiency with IgA deficiency (3.7%) and hyper-IgM (3.7%). In addition to antibiotics and intravenous immunoglobulin (IVIG) as a treatment for hypogammaglobinemia, twelve patients received IBD treatment during the follow-up period, of whom two were on 5-aminosalicylic acid, one on corticosteroids, three on immunomodulatory, four on anti-tumor necrosis factor, and two on vedolizumab. By the end of the follow-up [44.5 months (IQR 18-81)] 21 of 27 (77%) patients were in clinical remission.

CONCLUSION

This case series illustrates a strong male and CD-like features predilection. The diagnosis of IBD-like features mainly occurs after that of hypogammaglobulinemia, the majority of cases successfully recovered after appropriate treatment.

Key Words: primary hypogammaglobinemia, immunodeficiency, inflammatory bowel disease, IBD-like features

Introduction

Inflammatory bowel disease (IBD), primarily encompassing ulcerative colitis (UC) and Crohn's disease (CD), is an idiopathic disorder of the gastrointestinal (GI) tract that results from a complex interplay of environmental factors, abnormal gut microbiome, and dysregulated immune responses in genetically susceptible individuals(1,2). In Some cases, other conditions can mimic IBD and have clinical and endoscopic features that resemble those of IBD.

Hypogammaglobulinemias are heterogeneous diseases of either primary origin (genetic disorders and/or chromosome anomalies) or secondary origin (induced by extrinsic factors: infectious agents, mediators such as corticosteroids, immunosuppressant, chemotherapy, metabolic diseases such as nephrotic syndrome, and nutritional disorders). In adults, the two most common forms of primary Hypogammaglobulinemia are common variable immune deficiency (CVID) and selective IgA deficiency(3,4).

Infections causing chronic diarrhea, commonly related to parasitic infection mainly Giardia lamblia, occur with increased frequency because lack of immunoglobulins allows for attachment and proliferation of organisms on the intestinal epithelium (5–7).

Inflammatory bowel disease resembling CD or UC has been reported in CVID cohorts and other hypogammaglobulinemias with weight loss, chronic diarrhea, rectal bleeding, abdominal pain, and malabsorption (8–10). IBD-like features are typically diagnosed after the diagnosis of hypogammaglobulinemias. Endoscopic features include longitudinal ulcers and cobblestone appearance. Histologically, it can mimic lymphocytic colitis, collagenous colitis, and colitis-associated with graft-versus-host disease (11,12).

Immunoglobulin replacement does not ameliorate IBD-like disease, and the use of corticosteroids increases infectious susceptibility. Treatment of associated infection includes antibiotics to eliminate bacterial overgrowth, oral budesonide, 5-aminosalicylate agents, mercaptopurine (6MP), and azathioprine (AZA) (8,13). These medications do not significantly compromise immune function and immunoglobulin replacement helps protect patients from infectious complications to some degree. Gut inflammation is often difficult to control and unresponsive to standard IBD therapies. Targeted biological therapies, such as infliximab, adalimumab, vedolizumab, and ustekinumab, have been used with some benefit in cases of severe enteropathy; however, patients with significant T-cell defects require monitoring for fungal infections, and the duration of treatment is not established (9,14–18).

In these collaborative case series, we aimed to describe primary hypogammaglobulinemia patients with IBD-features and try to elicit the impact of the treatment and outcome.

Results

IBD-like characteristics

This report includes 27 patients with primary hypogammaglobulinemia and IBD-like features from 14 different centers; 20 males with a median age of 44 years (IQR 35-5-58.7) and 7 females with a median age of 50 years (IQR 30.4-81.9). 23 patients had CD-like features and 4 patients UC-like features. Two of the 4 UC-like features patients had pancolitis (Montreal classification E3, 50%), while most of the CD-like features showed either ileal (14 patients, 60.8%) or ileocolonic (9 patients, 39.2%) disease localization. The median age at IBD-like features presentation was 45.6 years (IQR 35.2-59). Eighteen patients were Caucasians (66.6%) and 3 patients (11.1%) had a positive family history of IBD. Only 3 patients (11.1%) were current smokers. Reported IBD treatments before the hypogammaglobulinemia diagnosis mainly consisted of 5-aminosalicylic acid (5-ASA) (1 patient, 3.7%), azathioprine/6-mercaptopurine (AZA/6MP) (2 patients, 7.4%), and anti-tumor necrosis factor (TNF) therapy (1 patient, 3.7%). One patient (3.7%) underwent prior surgery (small bowel resection).

Extraintestinal manifestations (EIMs) were described in seven patients [4 cases of peripheral arthropathy including one of them have also episcleritis and another one have axial arthropathy, 1 erythema nodosum, 1 pyoderma gangrenosum, and one with ankylosing spondylitis]. Patients' characteristics are described in Table 1.

Hypogammaglobulinemia characteristics

Primary hypogammaglobinemia etiologies were: common variable immunodeficiency (18 patients, 66.6%), agammaglobulinemia (2 patients, 7.4%), selective IgA-deficiency (3 patients, 11.1%), Goods syndrome (2 patients, 7.4%), IgG subclass deficiency with IgA deficiency (1 patient, 3.7%) and Hyper IgM (1 patient, 3.7%). The main symptoms were respiratory and gastrointestinal infections (20 patients, 74%), other infections include 2 cases of bacterial meningitis and two herpes zoster infection. Five cases of malignancy were described (1- Chronic lymphocytic leukemia (CLL), 1- intestinal lymphoma, 2-thymoma (one of them has also renal cell carcinoma), and one gastric cancer). Only one granulomatous disease was described (Granulomatous lung disease). The main treatment was antibiotics (18 patients, 66.6%) and intravenous immunoglobulin (IVIG) (22 patients, 81.4%), and one patient underwent a bone marrow transplant. All the patients had abnormal immunoglobulins levels: Twenty-one patients (77.7%) had abnormal IgA levels, 19 (70.3%) abnormal IgG levels, and 17 (62.9%) had abnormal IgM levels. The primary hypogammaglobulinemia characteristics are described in Table 2.

Twenty two patients had available data about the disease activity at the hypogammaglobulinemia diagnosis time: ten patients (45.4%) had clinical and endoscopic active gastrointestinal disease and 12 (54.6%) patients had no active

disease. Twelve of 16 patients (75%) with available C-reactive protein (CRP) had an elevated CRP level.

During the follow-up period [median 44.5 months (IQR 18-81.75)] eighteen patients received IBD-targeted therapy. Five patients recquired a short course of steroid [3 – systemic steroids and 2- low bioavailability steroids] and thirteen patients received persistent therapy, of whom two were on 5-aminosalicylic acid, one on corticosteroids, three on immunomodulatory (AZA), four on anti-tumor necrosis factor (3-adalimumab,1- infliximab), two on vedolizumab and one on Total Parenteral Nutrition (TPN). By the end of the follow-up, 21 of 27 (77%) patients were with no gastrointestinal symptoms , eight of them were on active IBD-targeted therapy. The 4 patients who received IBD targeted therapy before the hypogammaglobulinemia diagnosis continued the same treatment and 3 of them were in clinically remission and one had active GI disease.

Thirteen patients had a recurrent infection, five of them had multiple pathogens (Campylobacter jejuni, Giardia lamblia, Clostridium difficile, and Cytomegalovirus). In addition to antibiotics and intravenous immunoglobulin (IVIG) as a treatment for hypogammaglobinemia, six out of the 13 patients were on IBD targeted therapy [3- patients on steroids, 1- AZA, 1- vedolizumab, 1- adalimumab, and one patient on TPN].

During the fellow up period, nine patients underwent gastrointestinal surgeries: two patients underwent small bowel resection, 4- ileocecal resection, 2- colectomy, and one-distal gastrectomy for cancer. Six of these nine (66.6%) patients have recurrent GI- symptoms after the operation, two patients have no recurrent symptoms, and one patient died (due to gastric cancer). All death cases (3/27- 11.1%) were secondary to the hypogammaglobulinemia and infection, including the patient with gastric cancer how died due to septic shock after surgery.

Discussion

In adults, the most common form for primary hypogammaglobulinemia is common variable immune deficiency (CVID). The most gastrointestinal manifestations are chronic diarrhea, weight loss, and malabsorption. In some cases, it's can mimic IBD and it is difficult to distinguish from IBD even in clinical and endoscopic aspects (8,10). A cohort of patients with CVID was shown to have reduced bacterial diversity and increased levels of plasmatic lipopolysaccharide and pro-inflammatory soluble CD25. Interestingly, these findings were most pronounced in the subgroup of CVID patients with immune dysregulation including IBD (19). Autoimmune phenomena occur with some frequency in patients with hypogammaglobulinemia. Specifically, in CVID it has been observed in a group of patients that activation of tumor necrosis factor-alpha (TNFα) persists, contributing to the onset of inflammatory bowel disease in these patients (20). Another explanation for IBD-like symptoms in immunodeficient patients is defects in T-and B-cell function, more than 80% of patients have normal numbers of B lymphocytes, but when the lymphocytes are presented with an antigen, they fail to

differentiate into antibody-secreting plasma cells (21). In our series, 66.6% [18/27] of the cases were CVID, the most feature was CD-like feature [10 ileal, 8 colonic involvements] and two have UC-like feature [1-proctitis, 1-pancolitis].

Beside Infections causing chronic diarrhea, IgA deficiency is associated with various autoimmune and inflammatory disorders of the gut. A 10- to 20- fold increase risk for celiac in selective IgA deficiency has been reported. The link between these diseases may be genetic through shared HLA haplotypes (7). IBD, mostly ulcerative colitis, have also been reported in association with selective IgA deficiency (22–24). In this study cohort, we reported 3 cases of selective IgA deficiency (11.1%) with IBD-like features two of them had ulcerative colitis-like features. In one review about the rare constellation of thymoma and hypogammaglobulinemia (Good syndrome), ulcerative colitis as a cause of diarrhea was described in 2 cases, while immune-mediated colitis as a cause of diarrhea was also suggested in 2 more cases. In the literature, we found also 2 more cases in an association of Chron's disease like manifestations (25–28). In this case series, we described 2 cases of Goods syndrome with CD-like features, too.

The diagnosis of hypogammaglobulinemia was made before the IBD-like features diagnosis in 20 patients (median of 7 years prior, IQR 2.6-20.6years), and after IBD-like features appearance in 7 cases (median of one year after, IQR 0.45-5.6 years).

The most common infectious manifestations are respiratory and gastrointestinal infection as is known in hypogammaglobinemias (29–31). Also, hypogammaglobulinemia can be associated with many different autoimmune conditions [most commonly pmmune thrombocytopenic purpura and hemolytic anemia followed by psoriasis, autoimmune thyroiditis, autoimmune atrophic gastritis, rheumatoid arthritis, and Evans syndrome] (32,33). In our cohort 12 of 27 cases had autoimmune conditions [3- Evans, 1- Autoimmune hemolytic anemia, 2- rheumatoid arthritis, 2- psoriasis, 1- Sjogren syndrome, 4-celiac-like enteropathy (three of the celiac-like have multiple AI-conditions: 1- autoimmune gastritis and amyloidosis, 1- diabetes type 1 and autoimmune gastritis and one associated also with Evans syndrome)].

In general, an appropriate treatment with IVIG and antibiotics can control disease exacerbation, recurrent infections, and symptoms, however, gastrointestinal diseases are not treated with immunoglobulin because preparations contain IgG, which cannot reach the lumen of the intact gut. Treatment with oral immunoglobulin has not been successful because IgG is rapidly destroyed before reaching the small intestine (34–36). Currently, treatment for gastrointestinal manifestations in antibody deficiency syndromes is guided by successful therapy used for similar disorders in immunocompetent patients, with additional caution when immunosuppressive agents are administered (35). In our series 5 patients reacquired a short course of steroid and thirteen patients received persistent IBD-targeted therapy, of whom four on anti-TNF, one on vedolizumab, and one on received multiple biologic class without

response and underwent total colectomy two years after the diagnosis and still with active GI- symptoms.

Our study has several limitations: it was a retrospective case report data collection, and it relied on voluntary submission of cases by physicians who responded to the ECCO calls and therefore might be subject to geographical and selection biases. Histological data were not available. Due to the low sample size, the correlation between IBD targeted therapies and outcome is challenging to assess. Also, no risk factors or predictors can be investigated.

In conclusion, these case series of primary hypogammaglobulinemia with IBD-like features illustrates a strong male and CD-like features predilection. The diagnosis of IBD-like features mainly occurs after that of hypogammaglobulinemia, the majority of cases successfully recovered after appropriate treatment including immunomodulators and biologic therapy. Adding biological therapy may be safely practiced in some patients. However, until further data are available, this needs to be a case-by-case decision after careful weighing of the infectious and immunological state as well as the disease activity in the individuals.

Table 1.

Patients demographics and characteristics.

characteristics	Value (*n* = 27)
Age (in years)	48 (21-86)
Sex , n(%)	
Female	7(26%)
Male	20 (74%)
Age at IBD-features appearance (years)	41.5 (11-80)
Age at hypogammaglobulinemia diagnosis (years)	33.4(2.1-77.7)
Smoking: current/past/never/unknown , n(%)	3 (11.1%) / 3 (11.1%) / 19(70.3%) / 2(7.4%)
Positive family history of IBD , n(%)	3 (11.1%)
IBD-like-features characteristics, n(%)	
Montreal classification—age (<16,17–40, >40 years)	3 (11.1%) / 15 (55.5%) / 9 (33.3%)
CD-Montreal classification—location (L1,L3)	14 (51.8%) / 9 (33.3%)
UC-Montreal classification—location (E1, E2, E3)	1 (3.7%) / 1 (3.7%) / 2 (7.4%)
Perianal disease , n(%)	1 (3.7%)
Race , n(%)	
Caucasian	19(70.3%)
Black	1 (3.7%)
Arab	1 (3.7%)
Geographical spread , n(%)	
Italy	8 (29.6%)
Poland	8 (29.6%)
Israel	4 (14.8%)
Netherland	2 (7.4%)
Belgium	2 (7.4%)
Greece	2 (7.4%)
Switzerland	1 (3.7%)

IBD, inflammatory bowel disease (IBD); UC, Ulcerative colitis; CD, Crohn's disease.

Table 2.

Characteristics of primary hypogammaglobulinemia

Age at primary hypogammaglobulinemia diagnosis (years)	33.4(2.1-77.7)
Ethiologie, n (%)	
Common variable immunodeficiency disease	18 (66.6%)
Selective IgA deficiency	3 (11.1%)
Agammaglobulinemia	2 (7.4%)
Goods syndrome	2 (7.4%)
IgG subclass deficiency with IgA deficiency	1 (3.7%)
Hyper IgM	1 (3.7%)
Immunoglobulines level, n (%)	
IgG level (normal / abnormal / unknown)	3 (11.1%), 21 (77.7%), 3 (11.1%)
IgA level (normal / abnormal / unknown)	1 (3.7%) / 19 (70.3) / 7 (26%)
IgM level (normal / abnormal / unknown)	4 (17.8%) / 17 (63%) / 6 (22.2%)
Infections, n (%)	
Isolated respiratory infections	3 (12.5%)
Isolated gastrointestinal infections	3 (12.5%)
Respiratory and gastrointestinal infections	14 (58.3%)
Herpes zoster	2 (8.3%)
Bacterial meningitis	2 (8.3%)
Autoimmune mainifestations, n (%)	
Autoimmune hemolytic anemia (AIHA)	4 (20%)
Immune thrombocytopenia (ITP) *	3 (15%)
Rheumatoid arthritis	2 (10%)
Psoriasis	2 (10%)
Celiac-like enteropathy §¥¶	4 (20%)
Autoimmune gastritis (AIG) ¥¶	2 (10%)
Type 1 diabetes (T1D) ¥	1 (5%)
Amyloidosis ¶	1 (5%)
Sjögren's syndrome	1 (5%)
Granulomatous disease , n (%)	1 (3.7%)
Malignancy, n (%)	
Chronic Lymphocytic Leukemia	1 (16.6%)
Gastric cancer	1 (16.6%)
Thymoma	2 (12.5%)
Intestinal lymphoma	1 (16.6%)
RCC ₷	1 (16.6%)

IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M.

* , All cases of Immune thrombocytopenia (ITP) were associated also with Autoimmune hemolytic anemia (AIHA); §, A combination of several autoimmune conditions: Celiac-like enteropathy ,AIHA and ITP; ¥, A combination of several autoimmune conditions: B- Celiac-like enteropathy, Type 1 diabetes and Autoimmune gastritis; ¶, A combination of Autoimmune gastritis and Amyloidosis; ₷, combined with one case of thymoma.

Bibliography

1. Wallace KL, Zheng L-B, Kanazawa Y, Shih DQ. Immunopathology of inflammatory bowel disease. World J Gastroenterol. 2014 Jan 7;20(1):6–21.

2. de Souza HSP, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol. 2016 Jan;13(1):13–27.

3. 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 Feb;4(1):38–59.

4. Rose ME, Lang DM. Evaluating and managing hypogammaglobulinemia. Cleve Clin J Med. 2006 Feb;73(2):, 140, 143.

5. Eren M, Saltik-Temizel IN, Yüce A, Cağlar M, Koçak N. Duodenal appearance of giardiasis in a child with selective immunoglobulin A deficiency. Pediatr Int. 2007 Jun;49(3):409–411.

6. Atarod L, Raissi A, Aghamohammadi A, Farhoudi A, Khodadad A, Moin M, et al. A review of gastrointestinal disorders in patients with primary antibody immunodeficiencies during a 10-year period (1990-2000), in children hospital medical center. Iran J Allergy Asthma Immunol. 2003 Jun;2(2):75–79.

7. Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. Selective iga deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. Scand J Immunol. 2017 Jan;85(1):3–12.

8. Agarwal S, Smereka P, Harpaz N, Cunningham-Rundles C, Mayer L. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. Inflamm Bowel Dis. 2011 Jan;17(1):251–259.

9. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol. 2007 Dec;31(12):1800–1812.

10. Mannon PJ, Fuss IJ, Dill S, Friend J, Groden C, Hornung R, et al. Excess IL-12 but not IL-23 accompanies the inflammatory bowel disease associated with common variable immunodeficiency. Gastroenterology. 2006 Sep;131(3):748–756.

11. Washington K, Stenzel TT, Buckley RH, Gottfried MR. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Pathol. 1996 Oct;20(10):1240–1252.

12. Byrne MF, Royston D, Patchett SE. Association of common variable immunodeficiency with atypical collagenous colitis. European journal of …. 2003;

13. Elnachef N, McMorris M, Chey WD. Successful treatment of common variable immunodeficiency disorder-associated diarrhea with budesonide: a case report. Am J Gastroenterol. 2007 Jun;102(6):1322–1325.

14. Uzel g. complications of tumor necrosis factor blockade in chronic granulomatous disease-related colitis. Clin Infect Dis. 2010 Jan 1;51:1429–1434.

15. Chua I, Standish R, Lear S, Harbord M, Eren E, Raeiszadeh M, et al. Anti-tumour necrosis factor-alpha therapy for severe enteropathy in patients with common variable immunodeficiency (CVID). Clin Exp Immunol. 2007 Nov;150(2):306–311.

16. Vedolizumab in Patients With Common Variable Immune Defi ciency and Gut Infl ammation Long-term Combination Therapy with Anti-TNF plus ….

17. Klemann C, Pannicke U, Morris-Rosendahl DJ, Vlantis K, Rizzi M, Uhlig H, et al. Transplantation from a symptomatic carrier sister restores host defenses but does not prevent colitis in NEMO deficiency. Clin Immunol. 2016 Mar;164:52–56.

18. Uzzan M, Ko HM, Mehandru S, Cunningham-Rundles C. Gastrointestinal Disorders Associated with Common Variable Immune Deficiency (CVID) and Chronic Granulomatous Disease (CGD). Curr Gastroenterol Rep. 2016 Apr;18(4):17.

19. Kumar V, Jarzabek-Chorzelska M, Sulej J, Karnewska K, Farrell T, Jablonska S. Celiac disease and immunoglobulin a deficiency: how effective are the serological methods of diagnosis? Clin Diagn Lab Immunol. 2002 Nov;9(6):1295–1300.

20. Aukrust P, Lien E, Kristoffersen AK, Müller F, Haug CJ, Espevik T, et al. Persistent activation of the tumor necrosis factor system in a subgroup of patients with common variable immunodeficiency--possible immunologic and clinical consequences. Blood. 1996 Jan 15;87(2):674–681.

21. Tegtmeyer D, Seidl M, Gerner P, Baumann U, Klemann C. Inflammatory bowel disease caused by primary immunodeficiencies-Clinical presentations, review of literature, and proposal of a rational diagnostic algorithm. Pediatr Allergy Immunol. 2017;28(5):412–429.

22. Cunningham-Rundles C. Physiology of IgA and IgA deficiency. J Clin Immunol. 2001 Sep;21(5):303–309.

23. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol. 2009 Jan;29(1):130–136.

24. Agarwal S, Cunningham-Rundles C. Gastrointestinal manifestations and complications of primary immunodeficiency disorders. Immunol Allergy Clin North Am. 2019;39(1):81–94.

25. Kelesidis T, Yang O. Good's syndrome remains a mystery after 55 years: A systematic review of the scientific evidence. Clin Immunol. 2010 Jun;135(3):347–363.

26. Disselhorst MJ, Dickhoff C, Alhan C. Good's syndrome: an uncommon cause of therapy-resistant diarrhoea. Neth J Med. 2016 Aug;74(7):309–312.

27. Vázquez-Morón JM, Pallarés-Manrique H, Martín-Suárez IJ, Benítez-Rodríguez B, Ramos-Lora M. Crohn's-like disease in a patient with common variable immunodeficiency treated with azathioprine and adalimumab. Rev Esp Enferm Dig. 2013 Jun;105(5):299–302.

28. Mancuso A, Gentiluomo M, Vangeli M, Torre MD, Belli LS. Diarrhea as sole presentation of Good's syndrome mimicking Crohn's disease. Clin Immunol. 2013 Apr;147(1):9–10.

29. Kainulainen L, Vuorinen T, Rantakokko-Jalava K, Osterback R, Ruuskanen O. Recurrent and persistent respiratory tract viral infections in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol. 2010 Jul;126(1):120–126.

30. Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. Clin Microbiol Rev. 2009 Jul;22(3):396–414.

31. Rezaei N, Hedayat M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. J Allergy Clin Immunol. 2011 Jun;127(6):1329–41.e2; quiz 1342.

32. Hammarström L, Vorechovsky I, Webster D. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Clin Exp Immunol. 2000 May;120(2):225–231.

33. Cunningham-Rundles C. Autoimmunity in primary immune deficiency: taking lessons from our patients. Clin Exp Immunol. 2011 Jun;164 Suppl 2:6–11.

34. Nabavi M, Esmaeilzadeh H, Arshi S, Fallahpour M, Mortazavi N, Rezaei N. Could oral administration of immunoglobulin reduce diarrheal severity in common variable immunodeficiency? Allergol Immunopathol (Madr). 2014 Jul;42(4):371–372.

35. Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. J Allergy Clin Immunol. 2009 Oct;124(4):658–664.

36. Khodadad A, Aghamohammadi A, Parvaneh N, Rezaei N, Mahjoob F, Bashashati M, et al. Gastrointestinal manifestations in patients with common variable immunodeficiency. Dig Dis Sci. 2007 Nov;52(11):2977–2983.