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CASE SERIES

Hypogammaglobulinemia-associated gastrointestinal disease–A case series

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Abstract Hypogammaglobulinemia, a form of primary immunodeficiency, is an uncommon condition. Gastrointestinal (GI) symptoms may be the only presentation. A series of 22 patients who presented with GI symptoms and were diagnosed with hypogammaglobulinemia is presented. Chronic diarrhea was the presentation in majority (90.9 %) of patients. Malabsorption was identified in 87.5 % of patients followed by weight loss (59.0 %), abdominal pain (27.2 %), and oral ulcers (4.5 %). The median duration of symptoms prior to diagnosis was 4 years, range being 6 months to 23 years. Evaluation revealed opportunistic infections including *Giardia lamblia* in 31.8 % and *Cryptosporidium parvum*, *Isospora belli*, *Cytomegalovirus* and *Aeromonas* in 4.5 % each. Serum globulins were low in all patients. Duodenal biopsy showed paucity of plasma cells in 45 %, villous atrophy in 35 % and nodular lymphoid hyperplasia in 30 % patients. Though uncommon, hypogammaglobulinemia is associated with GI disease. The possibility of a primary immunodeficiency should be considered in patients presenting with GI symptoms and low serum globulin.

Keywords Chronic diarrhea · Common variable immunodeficiency · Immunodeficiency

Introduction

Hypogammaglobulinemia is an uncommon form of humoral immunodeficiency. A number of genetic defects give rise to this disorder. The disease is usually diagnosed late because of its variable presentation. Gastrointestinal (GI) symptoms are occasionally the only presenting symptom of this disorder. In this case series, we present the GI diseases associated with hypogammaglobulinemia.

Methods

Medical records of patients who attended the Gastroenterology Department at Christian Medical College, Vellore, India, in the last 10 years were retrospectively reviewed. Ethical clearance for the study was obtained from the Institutional review board (Research and Ethics committee) of Christian Medical College, Vellore, India.

Patients over the age of 4 years, who presented with GI symptoms and noted to have hypogammaglobulinemia, were included in the study. Hypogammaglobulinemia was diagnosed based on low IgG (<800 mg/dL), with or without concomitant decrease in IgA (<140 mg/dL) and/or IgM (<50 mg/dL). Clinical information and laboratory data were collected by a standardized review of medical charts and the data thus obtained was recorded in structured data forms. Continuous data is presented as median (±range) and as percentages as appropriate.

Results

Twenty-two individuals presenting with GI symptoms had associated hypogammaglobulinemia. The median age was 26 years. The characteristics of the patients included in this series are presented in Table 1. Almost all patients (20, 90.9 %) presented with chronic diarrhea.

The duration of symptoms prior to diagnosis ranged from 6 months to 23 years with a median duration of 4 years.

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Table 1 Characteristics and investigations of common variable immunodeficiency patients (n=22)

Demographic characters	Age, years	26 (10–46) [a]
	Male	20 (90.9) [b]
Symptoms	Chronic diarrhea	20 (90.9) [b]
	Malabsorption syndrome[‡] (n=8)	7 (87.5) [b]
	Weight loss	14 (63.6) [b]
	Pain abdomen	7 (31.8) [b]
	Recurrent LRTI	7 (31.8) [b]
	Oral ulcers	1 (4.5) [b]
Baseline characteristics	Hemoglobin, g/dL	11.3(7.2–4.7) [a]
	Total protein, g/dL	5.3 (3.4–6.6) [a]
	Albumin, g/dL	3.5 (2.2–5) [a]
	Globulins, g/dL	1.8 (0.9–2.6) [a]
	IgG[$], mg/dL	293 (<100–643) [a]
	IgA, mg/dL	<10 (<10–295) [a]
	IgM, mg/dL	<10 (<10–118) [a]
Opportunistic gastrointestinal infections	*Giardia lamblia*	7 (31.8) [b]
	Cryptosporidium parvum	1 (4.5) [b]
	Strongyloides	1 (4.5) [b]
	Isospora belli	1 (4.5) [b]
	CMV (gastritis, colitis)	1 (4.5) [b]
	Aeromonas	1 (4.5) [b]
Duodenal (D2) biopsy (n=20)	Paucity of plasma cells	9 (45) [b]
	Villious atrophy	7 (35) [b]
	Nodular lymphoid hyperplasia	6 (30) [b]
	Giardia lamblia	3 (15) [b]
	Isospora belli	1 (5) [b]

LRTI lower respiratory tract infection, *CMV* Cytomegalovirus

[$] Ig Immunoglobulin

[a] median (range)

[b] number (%)

[‡] Malabsorption syndrome was checked in eight subjects

History of recurrent lower respiratory tract infection (LRTI) was present in 6 (27.2 %) patients. One patient each had pedal edema with ascites, skin lesions of scabies and clubbing on examination. HIV ELISA, HCV antibody and anti-tTG were negative in all patients. HBsAg was positive in one patient (4.5 %). All patients had low IgG, 19 (86.3 %) had low IgA while 18 (81.8 %) had low IgM. Fifteen (68.1 %) of them had IgG levels below 500 mg/dL. Of the 22 patients, 17 (77.2 %) had combined deficiency of IgG, IgA and IgM, 4 (18.1 %) had IgG and IgA deficiency, and only 1(4.5 %) had IgG and IgM deficiency. Amongst these three combinations of immunoglobulin deficiency no significant difference was noted (Table 2). *Giardia lamblia* was noted in 7 patients (31.8 %) and appeared to be the most common opportunistic infection of gut. Eight patients were tested for urine xylose and 72-h stool fat. Of these patients, both urine xylose and 72-h stool fat was abnormal in 6 patients, while 72-h stool fat alone was abnormal in 1 patient. Of these 7 patients, parasitic infestation was identified in 6 (*G. lamblia* in 4 and *Cryptosporidium parvum* and *Isospora belli* in one each).

Esophagogastroduodenoscopy (EGD) was performed in 20 patients. EGD was normal in 9 (45 %), duodenal (D2) nodularity was noted in 7 (35 %), sessile polyps and granular duodenal mucosa in 1 (5 %) patient. Duodenal biopsy reports are summarized in Table 1. Ileal nodularity was noted in 7 (out of 12) patients on colonoscopy. Autoimmune enteropathy and *Cytomegalovirus* colitis was diagnosed in one patient each. Bronchiectasis was present in 4 (18.1 %).

Discussion

Hypogammaglobulinemia is an uncommon form of primary immunodeficiency disorder. In our study, the median age of presentation was 26 which are comparable with other studies. In one of the largest series of patients, the mean age at onset of symptoms was 23 years for males and 28 years for females; while the mean ages of diagnosis were 29 and 33 years, respectively [1].

In another series GI inflammatory disease, malabsorption and liver disease was present in 15 %, 6 % and 9 %,

Table 2 Characteristics based on immunoglobin deficiency profiles

Median (range), number (%)		Low IgG, IgA and IgM*	Low IgG and Low IgA only*	Low IgG and Low IgM only*
Total numbers (22)		17 (77.3)	4 (18.1)	1 (4.5)
Clinical symptoms	Chronic diarrhea	15 (88.2)	4 (100)	1 (100)
	Weight loss	11 (64.7)	2 (50)	1 (100)
	Pain abdomen	6 (35.3)	0	1 (100)
	Recurrent LRTI	6 (35.3)	1 (25)	0
	MAS‡	5 (83.3)	2 (100)	0
Opportunistic infections	*Giardia lamblia*	5 (29.4)	2 (50)	0
	Cryptosporidium parvum	1 (5.9)	0	0
	Strongyloides	0	1 (25)	0
	Isospora belli	1 (5.9)	0	0
	CMV (gastritis, colitis)	1 (5.9)	0	0
	Aeromonas	1 (5.9)	0	0
Duodenal biopsy	Paucity of plasma cells	8 (47.1)	1 (25)	0
	Villous atrophy	6 (35.3)	1 (25)	0
	Nodular lymphoid hyperplasia	4 (23.5)	2 (50)	0
	Giardia lamblia	3 (17.6)	0	0
	Isospora belli	1 (5.9)	0	0

LRTI lower respiratory tract infection, *CMV* Cytomegalovirus

*Number (%)

‡ MAS: (malabsorption syndrome) was checked in eight subjects

respectively [2]. Strober et al. reported that 50 % of their patients had chronic diarrhea with malabsorption [3]. In a case series of 14 patients by Singh et al., diarrhea was present in 92.6 %. Singh et al. reported chronic diarrhea (91.3 %) as most common presentation followed by weight loss (60.8 %) and pain abdomen (26.1 %) [4]. In our series, the most common GI manifestation was chronic diarrhea (90.9 %). Of those tested, 87.5 % had malabsorption, while 59.1 % presented with weight loss and 27.3 % presented with abdominal pain. Parasitic infestation including *G. lamblia*, *Cryptosporidium parvum*, and *I. belli* was identified in 85.7 % of patients with malabsorption. These organisms are known to produce chronic diarrhea and malabsorption in patients who are immunocompromised. Duodenal biopsy showed nodular lymphoid hyperplasia (NLH) in 30 % as compared to 16.7 % in a study from Ghoshal et al. who studied 12 patients with hypogammaglobulinemia and malabsorption. In their study, villous atrophy was noted in 50 %; while in our series, only 35 % had villous atrophy [5]. In our study we noted that most patients with hypogammaglobulinemia had combined deficiency of all three immunoglobulins, while only 5 had dual deficiencies. However, differences in presentation could not be assessed because of the small numbers in each group.

Common variable immunodeficiency (CVID) is a form of primary immunodeficiency characterized by hypogammaglobulinemia and has a heterogeneous clinical presentation including sinopulmonary, systemic bacterial infections and GI complications [6]. There is no universally accepted definition of CVID. The Pan American Group of Immunodeficiency (PAGID) and European Society for Immunodeficiencies (ESID) have suggested that CVID may be diagnosed in individuals over 4 years who have:

a. Significantly low total serum IgG
b. Poor or absent response to immunization
c. Exclusion of other causes of hypogammaglobulinemia [6]

In this present study, we have included patients aged more than 4 years with hypogammaglobulinemia with associated GI symptoms. However, we were limited by a lack of information regarding the response to vaccines in these patients. In patients with chronic diarrhea, low serum globulin levels should arouse a suspicion for a primary immunodeficiency. Limitations of our study include absence of vaccine data, referral bias and its retrospective nature.

Conflict of interest LD, RTK, EGS, AKD, AJJ, and SDC all declare that they have no conflict of interest.

Ethics statement The authors confirm that the study was performed in a manner that conforms with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights.

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