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CASE SERIES

Chronic diarrhea and malabsorption due to hypogammaglobulinemia: a report on twelve patients

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Abstract Hypogammaglobulinemic sprue (HGS), which may predispose to infection, is uncommon. Twelve patients (all men; median age 29 years, 15–50) with HGS (4%) of 296 with chronic small bowel diarrhea and malabsorption syndrome (MAS) during a 10-year period were analyzed. Treatment of HGS was delayed due to misdiagnosis as intestinal tuberculosis (n=7) and diarrhea-predominant irritable bowel syndrome (n=1). All had diarrhea and weight loss (median loss 12 Kg). Associated conditions were clubbing, bronchiectasis, and seizure (2 patients each), and hypothyroidism (n=1). Laboratory parameters were urinary D-xylose median 0.46 g/5 g/5 h (range 0.2–1.6; normal ≥1), fecal fat 11.9 g/day (3.8–16.7; normal ≤7 g), serum IgA, IgG, and IgM: 23.5 mg/dL (17–114; normal 90–450), 584 mg/dL (145–1051; normal 800–1800), and 23 (0–40.3; normal 60–280). IgA, IgG, and IgM were low in 10, 10, and 11, respectively. Duodenal biopsy was normal in 6 patients and showed partial villous atrophy in 6 and nodular lymphoid hyperplasia in two. Associated infections were giardiasis (n=1), disseminated strongyloidiasis (1), small intestinal bacterial overgrowth (3), septicemia (2), and septic arthritis (1). Two patients died of sepsis, five are well on immunoglobulin and specific anti-infective treatment, and five are lost to follow up. Approximately 4% patients with MAS have hypogammaglobulinemia, which is often associated with infection and is diagnosed late.

Keywords Common variable immunodeficiency syndrome · Gastrointestinal infection · Hypogammaglobulinemic sprue

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Introduction

Chronic small bowel diarrhea and malabsorption syndrome (MAS) are common disorders all over the world. MAS results from several diseases [1]. Hypogammaglobulinemic sprue (HGS) in adults has been described mostly as case reports and small series from temperate countries [2–4] and only as case report from India [5]. Though hypogammaglobulinemia predisposes to gastrointestinal and systemic infection and infestations [6], which are likely to be more common in developing countries, there is no systematic study on frequency and nature of infection and infestations in patients with HGS from developing countries. Therefore, we present a series of twelve consecutive adult patients with HGS from a tertiary referral hospital in northern India and frequency and nature of infection and infestation among them. One of these cases has been published earlier [7].

Table 1 Laboratory parameters of patients with hypogammaglobulinemic sprue

Laboratory parameter	Median	Range
Hemogram and serum proteins		
Hemoglobin (g/dL)	11.5	8–14
TLC (per mm^3)	9,800	4,400–18,000
Platelets (1000/mm^3)	228	71–568
Serum protein (g/dL)	5.8	3.2–8.0
Serum albumin (g/dL)	3.2	1.2–4.4
Serum globulin (g/dL)	2.9	1.5–4.0
Tests of malabsorption		
D-xylose excreted in urine (g)	0.46	0.23–1.64
Daily stool weight (g)	787	350–1350
Daily fecal fat (g)*	11.9	3.8–16.7
Serum immunoglobulin (n=12)		
Serum IgA (normal 90–450 mg/dL)	23.5	17–114
Serum IgG (normal 800–1800 mg/dL)	584	145–1051
Serum IgM (normal 60–280 mg/dL)	23	17–40

*72 h fecal fat was done in 8 patients

Methods

During a 10-year period (between 2000 and 2010), of 296 patients with chronic small bowel diarrhea and MAS attending Luminal Gastroenterology Clinic of the Department of Gastroenterology, 12 (4%) patients were diagnosed with HGS. Past medical records were examined to look for diagnosis and therapy received by the patients.

Diagnosis of HGS was made after work-up of all the patients with MAS based on a standard protocol reported previously [1]. Significantly low or a level below detectable limits in the serum of one or more immunoglobulin(s) (IgA, IgG, and IgM) was the basis for diagnosis of hypogammaglobulinemia.

Each patient was evaluated for gastrointestinal and systemic infection. Microscopic examination of three stool specimens was done to look for ova, cysts, or parasites. Histological evaluation of duodenal biopsy obtained at esophagogastroduodenoscopy was performed to look for *Giardia lamblia* and *Strongyloides stercoralis*. Upper gut aspirate obtained by a standard techniques described by us previously [8, 9] was used to culture for bacteria aerobically and anaerobically and colony count was performed; total count of bacteria $\geq 10^5$ colony forming unit per mL of aspirate was diagnostic of small intestinal bacterial overgrowth (SIBO) [8, 9]. A part of the aspirate was also examined microscopically for protozoa and *Strongyloides*. Each patient also underwent glucose and lactulose hydrogen breath test (*Lactoscreen*® H_2 breath tester, Hoek Loos, Amsterdam, Netherlands) [10]. A positive glucose hydrogen breath test and/or two peaks in lactulose hydrogen breath test were diagnostic of SIBO [10]. Chest radiograph was performed to look for bronchiectasis, pneumonia, or pulmonary tuberculosis as indicated. Sputum was examined using Gram's and acid fast stain (on three occasions) and cultured in patients with suggestive lesions at chest radiograph. In patients with fever, polymorphonuclear leukocytosis and toxic states, blood was cultured to document septicemia. In patients with persistent diarrhea, in whom attempts at findings a pathogen failed, at least three stool samples stained with modified acid fast stain and modified trichrome stain were examined for coccidian parasites. Stool was also examined for antigen of *Cryptosporidia* and *Giardia* in such situation based on clinician's decision.

Regular intravenous immunoglobulin was given every month with an aim to maintain a trough level of serum IgG above 800 mg/dL. Small bowel bacterial overgrowth was treated with oral norfloxacin (400 mg twice daily) or tetracycline (500 mg thrice daily) for 10 days every month. For parasitic infestations, specific therapies were given.

Results

All the twelve patients were men and most were young (median age 29 years, range 15–50) at diagnosis. All patients presented with watery diarrhea without blood, and none had abdominal pain. Stools were large volume, greasy, foul smelling, frothy, pale, and watery. Median (range) stool

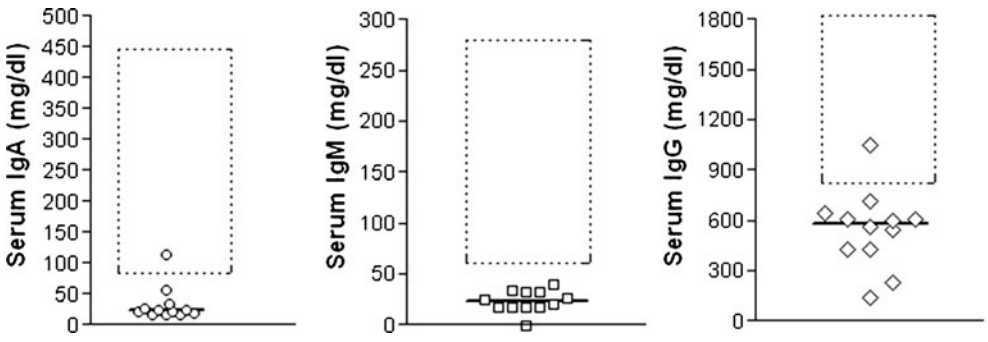

Fig. 1 Serum IgA, IgM, and IgG levels of patients with HGS at diagnosis. Rectangular-dashed line box is showing normal range while solid line drawn below the box is depicting median values

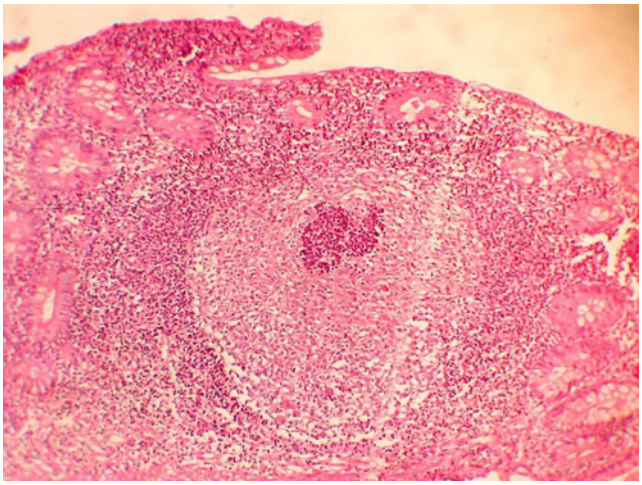

Fig. 2 Hematoxylin and Eosin stain of duodenal biopsy of a patient with HGS, showing NLH

frequency was 6.5/day (5–10). All patients had nocturnal diarrhea, which was frequent enough to disturb their sleep in nine patients, whereas three had occasional nocturnal stools (<3 per month). Median weight loss was 12 Kg (7–22). Median body mass index (BMI) was 15.6 Kg/m^2 (12.1–21.9 Kg/m^2). Clinical examination revealed clubbing in two, and hepatomegaly and splenomegaly in one patient each. Two patients had history of recurrent chest infections since childhood requiring repeated courses of antibiotics with bronchiectasis in one of them. Six patients had associated conditions including seizure (2), bronchiectasis (1), bronchial asthma (1,), *Herpes zoster* (1), and hypothyroidism (1). No patient had family history of similar illness.

Diagnosis was delayed in most patients; as median (range) age of symptom onset was 22.5 years (12–39) while age at diagnosis was 29 years (15–50). Before the diagnosis was established, seven patients (58.3%) were treated as gastrointestinal tuberculosis by a community physician (four were treated twice) and one (8.3%) was managed as diarrhea-predominant irritable bowel syndrome.

Laboratory parameters are summarized in Table 1 and Fig. 1. Malabsorption was diagnosed by urinary D-xylose (5 g) and 72-hour quantitative fecal fat estimation. D-xylose test was abnormal (<1.0/5 g/5 h) in 11 of 12 (91.7%) patients. Seventy-two hours fecal fat estimation revealed steatorrhea (>7 g/24 h) in eight patients who underwent this test. Barium small bowel series, done in eleven patients, revealed normal pattern in three, dilated bowel loops in two, small bowel mucosal fold thickening in six, along with dilated bowel loop and ulceration in one each. On esophagogastroduodenoscopy, three patients had reduced duodenal fold, and one had nodularity of duodenal mucosa. Duodenal biopsy revealed NLH in the latter patient. Among twelve patients, duodenal biopsy showed normal histology in six (50%), partial villous atrophy in six (50%) including NLH in two (16.7%, Fig. 2). Enzyme linked immunosorbant assay (ELISA) for human immunodeficiency virus and anti-endomysial antibody (EMA) was negative in all patients. Serum IgG, IgA, and IgM levels of individual patients are shown in Fig.1 and Table 2.

Table 2 Comparison of clinical and laboratory parameters of patients presenting with and without infections

Variables	Infection present (n=4)	No infection (n=8)	p-value
Clinical variables (median [range])			
Age (years)	31.5 (22–50)	27 (15–48)	0.39
BMI (Kg/m^2)	15.4 (14.5–21.9)	15.6 (12.1–21.8)	0.73
Duration (years)	4.0 (1–15)	4.0 (1–26)	0.80
Stool frequency (per day)	5.5 (5–8)	7.0 (6–10)	0.12
Weight loss	13.0 (10–22)	11.0 (7–15)	0.43
Laboratory variable (median [range])			
Hemoglobin (g/dL)	10.3 (8–11)	12.3 (10–14)	0.04
TLC (1000/mm^3)	9.1 (4.4–13)	10.3 (5.5–18)	0.50
Platelets (1000/mm^3)	211 (71–300)	238 (76–568)	0.50
Serum protein (g/dL)	5.5 (4.4–7.0)	6.2 (3.2–8.0)	0.44
Serum albumin (g/dL)	2.6 (1.2–3.3)	4.2 (1.2–4.4)	0.11
Serum globulin (g/dL)	3.3 (2.5–3.7)	2.7 (1.5–4.0)	0.396
D-xylose excreted in urine (g)	0.46 (0.23–0.95)	0.45 (0.24–1.64)	0.86
Serum IgA (normal 90–450 mg/dL)	24 (20–33)	23 (17–114)	0.61
Serum IgG (normal 800–1800 mg/dL)	556 (145–601)	607 (231–1051)	0.23
Serum IgM (normal 60–280 mg/dL)	17 (0–20)	29 (18–40)	0.04
Average daily stool weight (g)*	713 (450–1167)	1038 (350–1350)	0.77
Average daily fecal fat (g)*	9.3 (4.1–16.7)	14.4 (3.8–15)	0.56

*Stool fat and stool weight data are for four patients with, and four without infection

Among 12 patients, 4 had different bacterial, parasitic, and fungal infections. In two patients, stool examination revealed *Giardia lamblia*; in addition, one patient each had *Microsporidia* and *Strongyloides* infection. The patient with giardiasis and microsporidiasis also had recurrent respiratory tract infection and bilateral bronchiectasis, yeast-like cells in stool, and *E. coli*-related SIBO. The patient with strongyloidosis also had esophageal candidiasis, *E. coli* sepsis on blood culture, and polymicrobial SIBO (*E. coli*, *Streptococcus* species, *Pseudomonas aeruginosa*). Giardiasis improved with metronidazole, candidiasis responded to oral fluconazole, while microsporidiasis responded to albendazole therapy. In one patient, *P. aeruginosa* was grown on blood culture, and coagulase-negative *Staphylococcus* in sputum. In one patient, who had septic arthritis of knee joint, *P. aeruginosa* was isolated from synovial fluid and jejunal aspirate cultures (SIBO). Overall, three patients had SIBO and all of them responded to antibiotic therapy.

We had adequate follow up for five patients only, who remained symptom free during a median follow up period of 80 months (range: 18–216); two died of overwhelming sepsis within one month after first presentation, and five were lost to follow up after median period of nine months (range: 1–60).

Discussion

The present retrospective study suggests that hypogammaglobulinemia is not an uncommon cause of MAS in India. The diagnosis in this series of patients was delayed due to misdiagnosis as abdominal tuberculosis, a common condition in the tropics and diarrhea-predominant irritable bowel syndrome. Multiple bacterial and parasitic infections are common in these patients.

We could find only two previously reported patients on HGS from India, one of whom has been included in this series [5, 7]. There could be several possible explanations for the long delay in diagnosis in these patients. Firstly, hypogammaglobulinemia is a poorly recognized entity as a cause of MAS, leading to its misdiagnosis as intestinal tuberculosis, which is common in tropical countries. Some of our patients were treated for tuberculosis more than once. The non-availability of diagnostic serum immunoglobulin levels assay at several places may also account for delay in some cases. Lastly, even after finding hypogammaglobulinemia, clinicians may consider it to be secondary hypogammaglobulinemia (i.e., leaky gut resulting in low globulins). However, most of our patients had lower globulin than albumin values (Table 1).

One of the causes for hypogammaglobulinemia is common variable immunodeficiency disorder (CVID) which is diagnosed on the basis of reduced levels of two serum immunoglobulins, IgG and IgA, and/or IgM, at least two standard deviations below mean values, and impaired specific antibody production as evidenced by absent isohemagglutinins, poor responses to protein (diphtheria, tetanus), or polysaccharide vaccines (*S. pneumoniae*), or both [11]. Our patients did not have a complete etiological work-up, but it is possible that a few of our patients might have had CVID.

The bowel is exposed to multiple antigens including gut microbiota and pathogens from the environment. Locally secreted IgA plays a major role to contain these microbes [12]. Hence, it is not surprising to see increased susceptibility to infections including sino-pulmonary infections, systemic bacterial infections, and gastrointestinal infections and infestations. In our series, almost a third of the patients had one or more infections. Two patients had history of recurrent pulmonary infections since childhood, two had septicemia, and one each had giardiasis and strongyloidosis. Impaired humoral immunity of gut mucosa promotes bacterial contamination of small bowel, resulting in SIBO [13]. We found SIBO in three patients. Almost all our patients had low levels of one or more immunoglobulins in the blood.

This study highlights that hypogammaglobulinemia should be considered in the differential diagnosis of MAS in developing countries, particularly in a patient with recurrent sino-pulmonary or gastrointestinal infections, low serum globulin level, duodenal nodularity, or duodenal biopsy showing nodular lymphoid hyperplasia.

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