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Crohn's-like ileo-colitis in patients affected by glycogen storage disease Ib: two years' follow-up of patients with a wide spectrum of gastrointestinal signs

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Aim: To investigate the presence of inflammatory bowel disease (IBD) and to evaluate the progression of bowel involvement after two years' follow-up in seven patients affected by glycogen storage disease type Ib (GSDIb). *Methods:* Seven patients (5F, 2M, aged 4.5–20.6 y) entered the study. Bowel involvement was evaluated by ileocolonoscopy and specific IBD serologic markers. To evaluate disease activity, Paediatric Crohn's Disease Activity Index (PCDAI), terminal ileum wall thickness detected at ultrasonography (US), ^{99m}Technetium labelled autologous White Cell Scan (Tc-WCS) and barium meal with follow-through were investigated. *Results:* Ileocolonoscopy and histology examination revealed variable degrees of bowel involvement in all patients. The results of serologic markers were indicative of a Crohn's-like ileocolitis. US and Tc-WCS, could clearly define patients with severe inflammatory involvement, but failed to identify all patients with mild to moderate disease. For the most severely affected patients, anti-inflammatory agents and steroids were prescribed, whereas nutritional therapy with polymeric formula and antibiotics were assumed by two other patients and antibiotics only by one patient. Granulocyte colony-stimulating factor (G-CSF) was prescribed to all patients. Ileocolonoscopy and histology data improved in all patients. The assumption of G-CSF and/or gastric drip feeding (g.d.f.) was inversely associated with the PCDAI results ($p < 0.05$).

Conclusion: IBD is common in patients affected by GSDIb independently of the severity of gastrointestinal signs and symptoms. Different therapeutic approaches can be used according to the severity of IBD. G-CSF treatment and g.d.f. can be protective factors for IBD.

Key words: *Crohn's disease, G-CSF, glycogen storage disease Ib, neutropenia*

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Glycogen storage disease type I (GSDI) is a heterogeneous group of genetic disorders with an incidence of approximately 1/100 000 live births. Two major forms of the disease have been identified: GSDIa, due to mutations in the glucose-6-phosphatase (G6-Ptase) gene (1) and GSDIb, caused by mutations in the gene encoding for the microsomal glucose-6-phosphate (G6-P) translocase (2). Both GSDIa and GSDIb share common clinical and biochemical features, such as hypoglycaemia, hyperlactic acidaemia, dyslipidaemia, hyperuricaemia, hepatomegaly and kidney enlargement. GSDIb patients also suffer from mouth ulcers, perianal lesions and recurrent pyogenic infections due to neutropenia and functional deficiencies of neutrophils and monocytes (3, 4). The diagnosis of both GSDIa and Ib is presently reliant on molecular analysis (5). The treatment of the metabolic derangement is based on dietary therapy, including frequent meals, supplementation with cornstarch and nocturnal gastric drip feeding (g.d.f.) (6, 7). Granulocyte colony-stimulating factor (G-CSF) is used to restore the neutrophil count and improve neutrophil function in GSDIb patients (8). Crohn's-like colitis has been reported in GSDIb patients with severe clinical signs of bowel disease (9–11).

Idiopathic Crohn's disease (CD) is a chronic and recurrent inflammatory bowel disease (IBD) which could involve all parts of the gastrointestinal tract (12). The diagnosis is suspected on the basis of clinical signs such as weight loss, decreased height velocity, abdominal pain, perianal lesions, chronic diarrhoea and anaemia (13, 14). The diagnosis is usually performed by endoscopy and histology (15). To evaluate disease activity, other approaches have been used such as the Paediatric Crohn's Disease Activity Index (PCDAI) (16), study of ileal wall thickness at ultrasonography

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(US), barium meal with follow-through and ^{99m} Technetium white cell scan (Tc-WCS) (17–20). Recently, anti-*Saccharomyces Cerevisae* antibodies (ASCA) and perinuclear staining anti-neutrophil cytoplasmic antibody (pANCA) have been increasingly used for the evaluation of patients with IBD. Immunoglobulin (Ig)A and/or IgG ASCA show a high diagnostic specificity for CD (>90%) and a sensitivity of about 50%; they have been found in 50–60% of CD patients, 10 to 15% of ulcerative colitis (UC) patients and in less than 5% of healthy controls. Conversely, pANCAs have been described in 60–80% of UC patients, with a high degree of disease specificity (21, 22). Therapeutic protocols for CD are based upon immune suppressants and anti-inflammatory agents that can be associated with antibiotics (23–25). Several studies have shown the role of nutritional therapy in the treatment of the disease (26). The efficacy of whole-protein enteral feeding with polymeric formula has been reported (27). In the current study, we enrolled seven GSDIb patients independently from the presence of signs indicative of gastrointestinal disease to investigate the presence and the prevalence of IBD. We also evaluated the progression of bowel involvement after the two-years' follow-up.

Patients and methods

Patients

All the patients with GSDIb followed at the Department of Paediatrics, "Federico II", University of Naples, were included in the study. That is, seven GSDIb patients (5F, 2M, age range: 4.5–20.6 y, mean: 10.7 ± 6.2 y; median: 8.5 y) entered the study, after informed consent had been obtained and the study protocol had been approved by Local Ethics Committee. These patients were in follow-up for a period ranging from 6.5 to 19.1 y (mean 10.5 ± 5.6 y and median follow-up: 8 y). Patients' profiles are presented in Table 1.

Study design

Bowel involvement was evaluated by ileocolonoscopy, ASCA and pANCA. To evaluate disease activity, PCDAI, US, Tc-WCS and barium meal with follow-through were used. The results of the examinations were correlated to the most important clinical and biochemical features associated with GSDIb that could be considered as possible risk factors for developing IBD. The evaluation of bowel involvement was performed at study entry and after two years of follow-up.

Methods

Investigation for inflammatory bowel disease. Ileocolonoscopy was performed using a paediatric videocolonoscope (Olympus, Torino, Italy), with the patient sedated with Diazepam and Meperidine. The entire large bowel, including the caecum, ileocaecal valve and at least 20–30 cm of the terminal ileum, was explored. The intestine was divided into five segments: rectum, sigmoid and left colon, transverse colon, right colon and ileum, and the bowel involvement was considered as absent, mild, moderate or severe, according to the following data collected for each segment: the presence of mucosal lesions (pseudopolyps, healed ulcerations, frank erythema, swollen mucosa, aphthoid ulcerations, superficial or deep ulcerations), stenosis with or without ulcerations and the percentage of the segmental surface involved by the disease and by ulcerations. In each patient 8 to 12 biopsies were taken from the caecum, ileocaecal valve, terminal ileum and colon–rectum, with a median number of 10 specimens/patient. Intestinal biopsies were fixed in 10% formalin, dehydrated, paraffin embedded and routinely stained with haematoxylin and eosin. The biopsies were read and classified by an experienced pathologist who was unaware of the patient's diagnosis, disease history or macroscopic findings. The colon and ileum were evaluated as different segments. The inflammatory process was described as absent, mild, moderate or severe according

Table 1. Patients' clinical and biochemical features at first evaluation for inflammatory bowel disease.

	Sex	Age (y)	Age at diagnosis (mo)	Diet	Compliance to the diet	Admissions for hypoglycaemia	Admissions for infections	Neutrophil count median value (range) $\times 10^9$/L.N.V. 1.500–3.000	Duration of neutropenia (y)	G-CSF therapy
1.	F	4.5	7	Corn starch + g.d.f.	H	R	F	0.823 (0.335–4.388)	1.5	+
2.	F	6.3	1	g.d.f.	H	R	F	1.160 (0.630–4.230)	0.5	+
3.	M	6.5	3	Corn starch + g.d.f.	H	F	R	1.410 (0.690–4)	0.5	+
4.	M	8.5	6	Corn starch	H	R	F	0.753 (0.396–1.520)	7	–
5.	F	10.5	7	Corn starch	H	R	R	0.550 (0.280–1.460)	8.5	–
6.	F	18.4	5	Corn starch	L	R	R	0.275 (0.150–0.4)	16	–
7.	F	20.6	18	Corn starch + g.d.f.	H	F	F	0.579 (0.150–2.500)	13	+

Patient 6 started dietary treatment at the age of 18 y. Patient 7, stopped g.d.f. when she was 16 y old. Neutrophil count median value and duration of neutropenia were calculated before G-CSF therapy was started.

g.d.f.: gastric drip feeding; G-CSF: granulocyte colony-stimulating factor; +: performed, −: not performed; F: frequent; R: rare. H: high; L: low.

to the combined presence of the following parameters: epithelial damage and inflammatory cells infiltration involving the lamina propria or submucosa.

We used a well-established ELISA ASCAs assay, which has recently been evaluated in a large comparative study (21). Immunoglobulin A and IgG ASCA and IgG pANCA were determined by ELISA according to the instruction manuals (Medizym ASCA, ALIFAX, MEDIPAN Diagnostic, Selchow, Germany). The cut-off value used to discriminate between negative and positive IgA and IgG ASCA and pANCA IgG titres, as determined by the manufacturer on the basis of the results in well-defined patients with CD or ulcerative colitis, was set at 20 U/ml.

Serial trans-abdominal ultrasonographies (US) were performed to study both hepatomegaly and thickening of the terminal ileum. An ultrasound apparatus (Logiq MD 400, GE Medical System, Milan-Italy) with a linear transducer (7.5 MHz) was used. US was done in the morning, without any preparation, such as oral deflating drugs or water enema. The thickening of terminal ileum wall, the presence or absence of normal stratification of the intestinal wall and intramural vascularization were evaluated.

A Tc-WCS was performed using a dose of isotope scaled to the body surface area; autologous granulocytes were separated and labelled with ^{99m}Tc. Anterior and posterior abdominal images were obtained at 30 min, 1, 2, 3 h on a γ camera with a high-resolution collimator (General Electric, GE Starport 400 AT, USA), online with a computer (Microdelta Plus, Siemens, Germany). The scans were judged to be abnormal if radioactivity was seen in the gut within the first hour.

PCDAI was used only to evaluate inflammatory disease activity, although it has not been validated as a method for the assessment of the inflammatory disease activity in GSDIb patients. PCDAI is a numerical expression for the patient's degree of illness, composed of three items (history, physical examination and laboratory test), each shown to correlate with the physician's global estimate of the patient's illness. History was focused on the presence of abdominal pain, diarrhoea and limitation of activities; at physical examination, weight gain, height growth velocity, abdominal tenderness, perirectal disease and extra-intestinal manifestations were evaluated. Laboratory tests included haematocrit, erythrocyte sedimentation rate and serum albumin value. A PCDAI value below 10 was indicative of clinical remission, a value between 10 and 30 of moderate disease activity and a value above 30 of severe disease activity.

Clinical and biochemical features. GSDIb patients were admitted to the Department of Paediatrics every six months for follow-up of metabolic disease. The frequency of admissions to the hospital for hypoglycaemia and for severe infections was evaluated from medical records. Admissions were considered "rare" if less than one and "frequent" if more that one over six months. Clinical and biochemical investigations were aimed at evaluating the metabolic control (in particular blood pH and bicarbonate, lactic acid, glucose, uric acid and triglycerides) and the degree of neutropenia (expressed as nadir and median neutrophil count and duration of neutropenia) and neutrophil dysfunction. Nutritional and therapeutic regimens, prescribed for GSDI, and the compliance to the dietary treatment were also analysed. Compliance to the dietary treatment was evaluated by a daily diary recorded for three consecutive days and examined during the follow-up; moreover, a questionnaire including information regarding accuracy in the preparation of food, possible changes of diet programme and problems met in following the diet was also administered to the patients' parents every six months.

Statistical analysis. The statistical analysis was done using the Statistical Package for Social Science (SPSS 10.0 for Windows Update; SPSS Inc., Chicago, Illinois, USA). The possible association between the results of bowel investigations and possible risk or protective factors (neutropenia, dietary regimen and G-CSF therapy) was studied using the Spearman rank correlation coefficient. Significance was set at 5%.

Results

Investigation of inflammatory bowel disease

Bowel investigation at study entry. In Table 2 we show the clinical signs that are indicative of bowel involvement, and the results of bowel investigation by endoscopy and histology, serologic IBD markers, US, Tc-WCS. Barium meal with follow-through was normal in all patients. Detailed descriptions of endoscopical and histological findings are reported in Table 3. Aphtoid and linear ulcers were detected by ileocolonoscopy in four patients aged 4.5, 6.3, 8.5 and 10.5 y, respectively. Patient 1 showed superficial ulcerations in the left colon and a 2-mm apthoid ulcer in the caecum; patient 2 had deep ulcerations in the ileum and superficial ulcerations in the left and transverse colon; patient 3 showed friability of the mucosa of the ileum; patients 4 and 5 had deep ulcerations in the right, transverse, sigmoid and left colon and ileum; patient 7 showed hyperaemia of mucosa at the right, transverse, sigmoid and left colon. The PCDAI, used to evaluate disease activity, suggested severe activity in two patients and revealed moderate activity in three other patients. In our group of patients, the US findings paralleled the ileum involvement detected at histology ($r = 0.75$, $p = 0.04$).

The two patients with the most severe bowel involvement underwent therapy with steroids, anti-inflammatory and immunosuppressor agents and methronidazole according to the standard therapeutic

Table 2. Diagnostic approach to inflammatory bowel disease at the first evaluation (a) and after two years of treatment (b).

Patient	1		2		3		4		5		6		7	
	a	b	a	b	a	b	a	b	a	b	a	b	a	b
Decreased height velocity	–	–	–	–	–	–	+	–	+	–	+	–	–	–
Weight loss	–	–	–	–	–	–	–	–	+	–	–	–	–	–
Abdominal pain	–	–	–	–	–	–	+	–	+	–	–	–	–	–
Diarrhoea	–	–	–	–	–	+	+	–	+	–	–	–	–	–
Arthritis	–	–	+	+	–	–	+	–	+	–	–	–	–	–
Mouth ulcers	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perianal lesion	–	–	+	–	–	–	–	–	+	–	–	–	+	–
ASCA IgG	–	np	–	np	+	np	+	np	+	np	–	np	–	np
ASCA IgA	–	np	+	np	–	np	+	np	+	np	–	np	+	np
ANCA	–	–	–	–	–	–	–	–	–	–	–	–	–	–
US	+	–	+	+	–	–	+	+	+	+	–	–	–	+
Tc-WCS	–	–	–	–	–	+	+	–	+	–	–	–	–	–
Endoscopy	Mild	Normal	Moderate	Mild	Mild	Mild	Severe	Moderate	Severe	Mild	Normal	Normal	Mild	Moderate
Histology of ileum	Moderate	Mild	Moderate	Mild	Moderate	Mild	Severe	Mild	Severe	Mild	Moderate	Moderate	Mild	Mild
Histology of colon	Moderate	Mild	Moderate	Mild	Mild	Mild	Moderate	Mild	Severe	Moderate	Moderate	Moderate	Moderate	Moderate

IBD: inflammatory bowel disease; Tc-WCS: ^{99m}Technetium white cell scan; ASCA: anti-*Saccharomyces Cerevisae* antibodies; ANCA: anti-neutrophil cytoplasmic antibody; np: not performed. + = present or indicative of IBD; – = absent or not indicative of IBD; Tc-WCS + = marked focal accumulation of the tracer in the right lower quadrant; – = no focal accumulation of the tracer.

approach for CD. They also started the G-CSF treatment. For the patients with moderate activity, nutritional therapy with a polymeric formula (Modulen IBD, Nestlé, Vevey, Switzerland) and periodic administration of antibiotics were prescribed. Patient 7 assumed antibiotics but refused the elemental diet. G-CSF was started in patient 6 as the only therapy. Patients 1, 2, 3 and 7 were already receiving G-CSF treatment.

Patient 4 had to stop the therapy with an immunosuppressor agent because of leukopenia, whereas patient 5 developed a nephrotic syndrome probably due to the anti-inflammatory agents (28–30). No side effects were detected after antibiotics. Splenomegaly, probably caused by G-CSF, developed in four patients (2–4, 7).

Bowel investigation after two years. The results of bowel investigations are reported in Table 2. The ileocolonoscopy findings showed improvement of the inflammatory process in all subjects, with the exception of patient 7 (Table 3). However, in a more recent evaluation (after 3 y) only a very mild inflammatory involvement was detected in this patient. The PCDAI values did not suggest severe disease activity in any patient and revealed moderate activity in two patients (5, 7).

Clinical and biochemical features. The diagnosis of glycogen storage disease was performed in the first year of life in all but one patients. From the time of diagnosis, a specific dietary treatment was prescribed and a follow-up program was established. From the medical records, it appeared that the admissions to the hospital for hypoglycaemia were rare in 5/7 patients. All the patients suffered from frequent infections, but admissions were required for severe infections in 4/7 patients. Biochemical parameters of metabolic control were normal in all but one patient (6). No correlation was found among age, age at diagnosis, compliance with the diet, number of admissions for hypoglycaemia or severe infections, parameters of metabolic control and bowel involvement. The median value of neutrophil count and the assumption of G-CSF treatment were inversely associated only with PCDAI score ($r = -0.75$, $p = 0.04$ and $r = -0.87$, $p = 0.01$ respectively). Gastric drip-feeding assumption was inversely associated with PCDAI score ($r = -0.87$, $p = 0.01$).

Discussion

The association between Crohn's-like colitis and GSDIb has been reported elsewhere (9–11) in patients with severe clinical and biochemical signs of IBD. In the paper reporting the results of the European Study on Glycogen Storage disease, 20 patients with protracted diarrhoea (defined as diarrhoea for longer than 1 mo) with an increased daily stool frequency were described.

Table 3. Ileocolonoscopy and histology findings at first evaluation (a) and after 2 years of therapy (b).

	Endoscopy		Histology of ileum		Histology of colon	
	(a)	(b)	(a)	(b)	(a)	(b)
1.	Ileum: oedema	Ileum/colon: normal	Foci of inflammatory cells in the lamina propria	Infiltration of lymphocytes in the lamina propria	Foci of inflammatory cells in the lamina propria	Infiltration of lymphocytes and monocytes in the lamina propria
	Colon: aphtoid lesions; aphtoid ulcer in the caecum (2 mm diameter)					
2.	Ileum: aphtoid and linear ulcers	Ileum: atrophy of the mucosa	Foci of inflammatory cells in the lamina propria	Infiltration of lymphocytes in the lamina propria	Foci of inflammatory cells in the lamina propria	Mild infiltration of lymphocytes and plasmacells in the lamina propria
	Colon: hyperaemia and aphtoid lesions	Colon: hyperaemia				
3.	Ileum: friability of the mucosa	Ileum: friability of the mucosa	Foci of inflammatory cells in the lamina propria	Mild infiltration of lymphocytes and monocytes in the lamina propria	Infiltration of lymphocytes and monocytes in the lamina propria	Infiltration of lymphocytes and monocytes in the lamina propria
	Colon: normal	Colon: hyperaemia				
4.	Ileum: linear and aphtoid ulcers, fibrosis of ileocaecal valve	Ileum: aphtoid lesions	Severe infiltration of lymphocytes and monocytes extending to submucosa and muscolaris mucosae	Infiltration of lymphocytes and monocytes in the lamina propria	Mucosal atrophy and foci of inflammatory cells in the lamina propria	Infiltration of lymphocytes and monocytes in the lamina propria
	Colon aphtoid ulcers, friability	Colon: hyperaemia and friability				
5.	Ileum/colon: severe inflammatory pattern with linear and aphtoid ulcers, friability	Ileum/colon: hyperaemia and friability	Foci of inflammatory cells extending to submucosa and muscolaris mucosae; fibrosis of the muscolaris mucosae Vasculitis in the submucosa	Infiltration of lymphocytes and monocytes in the lamina propria	Severe infiltration of lymphocytes and monocytes in the lamina propria extending to submucosa and muscolaris mucosae Mucosal ulcers and cryptic abscesses Fibrosis and thickening of the muscolaris mucosae	Infiltration of lymphocytes and monocytes in the lamina propria Fat metaplasia of the submucosa
6.	Normal	Normal	Foci of lymphocytes and monocytes in the lamina propria extending to submucosa	Infiltration of lymphocytes and monocytes in the lamina propria extending to submucosa	Foci of inflammatory cells	Foci of inflammatory cells
7.	Ileum: mucosal atrophy	Ileum: mucosa atrophy	Infiltration of lymphocytes and monocytes in the lamina propria	Infiltration of lymphocytes, monocytes and eosinophils in the lamina propria	Infiltration of lymphocytes and monocyte in the lamina propria	Atrophy of the mucosa, infiltration of lymphocytes and monocytes in the lamina propria
	Colon: mucosal hyperaemia	Colon: aphtoid lesions			Fibrosis of the submucosa	Mucosal ulcers and cryptic abscesses

Of these patients, only 10 were evaluated by ileocolonoscopy, showing bowel involvement in all. Of these 10 patients, 7 underwent hemicolectomy and resection of the terminal ileum (9). The medical database of North American GSDIb patients identified 18 patients with chronic gastrointestinal symptoms; in particular, abdominal pain and/or obstructive symptoms were detected in 90% of the patients (11). These data underline that, until now, only patients with severe signs or symptoms indicative of bowel involvement had been investigated by ileocolonoscopy. In the current study, we showed that IBD is common in patients affected by GSDIb independently of the severity of gastrointestinal signs and symptoms, if any. The presence of the anti-*Saccharomyces cerevisiae* antibodies in 5/7 patients suggests that the inflammatory process is a Crohn's-like colitis, as reported elsewhere (11). Although endoscopy with histology examination is considered the "gold standard technique" for the diagnosis of IBD, we combined different approaches to investigate bowel involvement and the degree of inflammation. In our group of patients, we could clearly define patients with severe inflammatory involvement by using US and Tc-WCS, but these techniques failed to identify all patients with mild to moderate disease. For Tc-WCS, these results were probably related to the low amount of autologous granulocytes available for labelling, due to patients' neutropenia. The diagnostic accuracy of these techniques in patients affected by GSDIb and with mild to moderate bowel involvement should be studied in a larger population.

Different therapeutic approaches have been used according to the severity of inflammatory bowel disease. After two years, ileocolonoscopy readings showed improvement of the inflammatory process in all patients. These results suggest that, for severe IBD, anti-inflammatory agents are needed, whereas for mild to moderate disease activity, the combination of elemental diet with antibiotics and G-CSF could be sufficient in patients affected by GSDIb. These data are in agreement with previous data on idiopathic Crohn's disease (24–27). Side effects due to therapy were also observed in our patients. In particular, in association with immunosuppressant agents we observed leukopenia in one patient and nephrotic syndrome in another one. Nephrotic syndrome has been previously described in patients treated with mesalazine (28–30). Patients affected by GSDI (both types Ia and Ib) are at risk for kidney involvement (31, 32) characterized by hyperfiltration, glomerular sclerosis and terminal renal insufficiency. Thus, it might be suggested that anti-inflammatory agents contribute to the progression of renal disease in GSDI patients.

The pathogenesis of IBD in GSDIb patients is not clear. We analysed the hypothesis that the metabolic imbalance could be a risk factor for the development of bowel inflammation. Our results suggest that the metabolic alteration is not the cause of bowel damage. Indeed, GSDIa, with the same metabolic alteration of GSDIb, carries no apparent risk for IBD. Besides, neutropenia and/or neutrophil dysfunction could allow pathogenic or commensal enteric bacteria to infect the intestinal mucosa, leading to chronic inflammation. In our group of patients, the median value of the neutrophil count (and not duration of neutropenia or neutrophil nadir) was inversely associated with PCDAI score. These data could suggest that the neutrophil median value, rather than the duration of neutropenia or neutrophil nadir, plays an important role in the pathogenesis of inflammatory bowel disease. Furthermore, the efficacy of the G-CSF treatment on bowel involvement in GSDIb patients might be hypothesized on the basis of the association found between the assumption of G-CSF therapy and PCDAI score. The lack of detection of IBD in GSDIb patients born after the clinical availability of G-CSF (12) could confirm this hypothesis.

Several studies have shown the role of nutritional therapy in the treatment of CD (26). According to our results, patients who assumed g.d.f. had lower PCDAI scores compared with those of patients who refused this dietary treatment. This observation might suggest a protective role of the enteral feeding on bowel disease in GSDI patients.

In conclusion, our study shows that IBD is a common complication of GSDIb and should be considered even in the presence of mild clinical signs of intestinal disease. Different therapeutic approaches, including anti-inflammatory agents, antibiotic, nutritional therapy and G-CSF, could be proposed according to the severity of inflammatory bowel involvement. In the case of GSDIb patients, particular attention should be given to the side effects of the administered drugs. Dietary and therapeutic strategies such as g.d.f. and G-CSF seem to afford protection against IBD. Collaborative and controlled studies in a larger population are needed in order to provide definitive evidence supporting these hypotheses.

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