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Gastrointestinal Abnormalities among Patients with Chronic Granulomatous Disease

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Abstract

Objective: Chronic granulomatous disease (CGD) is characterized by increased susceptibility to infections and inflammation that may lead to various gastrointestinal (GI) abnormalities. Our objective was to better characterize the GI manifestations among patients suffering from CGD as well as the effects of different treatments.

Methods: We analyzed 11 patients with CGD managed by the immunology service at the Hospital for Sick Children, Toronto, Ontario between 2000 and 2012.

Results: All patients had one or more GI abnormality including colitis (72.7%), peri-anal fissure/abscess (36.3%) or oral aphthous ulcers (36.3%). Failure to thrive occurred in 5 patients (45.4%), all with associated colitis. Bone marrow transplantations (BMT) using HLA-identical sibling donors were performed in 4 patients, with 3 patients surviving. In these 3 patients, the inflammation-mediated GI manifestations present before BMT resolved during the follow-up period of 3.2-4.6 years. In contrast, 6 of 7 patients who did not receive BMT (p=0.033) continued to suffer from GI disease resulting in failure to thrive, GI bleeding and life threatening small bowel perforation and often required immune suppressive medications.

Conclusions: Inflammatory GI manifestations, particularly colitis, are very common in CGD and are often associated with significant morbidity. Allogeneic BMT, particularly if an HLA-matched sibling donor is available should be considered in patients with CGD who suffer from significant GI involvement.

Keywords: Chronic granulomatous disease; Inflammation; Gastrointestinal; Bone marrow transplantation; Morbidity

Abbreviations

CGD: Chronic Granulomatous Disease; GI: Gastrointestinal; BMT: Bone Marrow Transplantations; NOBI: Neutrophil Oxidative Burst Index

Capsule: Inflammatory gastrointestinal complications, particularly colitis, are very common among patients suffering from chronic granulomatous disease. The gastrointestinal abnormalities in patients with chronic granulomatous disease can be cured by allogeneic hematopoietic stem cell transplantations.

Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by impaired neutrophils production of reactive oxygen species secondary to defects in different components of the NADPH oxidase enzyme complex including the gp91phox (CYBB on chromosome Xp21.1), p47phox (NCF1 on chromosome 7q11.23), p67phox (NCF2 on chromosome 1q25), and p22phox (CYBA on chromosome 16q24). Mutations in the *CYBB* gene, which are transmitted by X-linked inheritance, are found in approximately 65-70% of North American patients with CGD and are typically associated with a more severe clinical phenotype [1]. Patients with CGD often suffer from infections caused by *Staphylococcus aureus, Burkholderia cepacia* complex, *Serratia marcescens, Nocardia spp*, *Aspergillus spp*, *Salmonella*, Bacille Calmette–Guérin (BCG) and tuberculosis, affecting organs such as the lungs, skin, soft tissues and bones [1]. Many patients also suffer from abnormal inflammatory response resulting in autoimmunity and granuloma formation. These granulomas may obstruct the urinary or gastrointestinal (GI) tract [1]. Additional GI manifestations including non-infectious colitis, enteritis, peri-anal disease, diarrhea, vomiting, aphthous ulcers and gingivitis are also common among patients with CGD [2-6]. The GI manifestations might lead to failure to thrive and require treatment with immune modulating medications, such as steroids, thalidomide, azathioprine, methotrexate and anti-TNF medications, thereby further increasing risk of infections and reducing quality of life [7,8].

Antibacterial and antifungal medications have been effective for prophylaxis and treatment of infections in patients with CGD [9-11]. Some have added interferon-gamma for treatment of infections or prophylaxis [12,13], although the long-term benefits are still not clear [14]. Allogeneic bone marrow transplantations (BMT) from HLA matched family donors with myeloablative or non-myeloablative preparation can cure the increased susceptibility to infections of CGD patients [15,16]. Autologous gene therapy has also been explored in limited number of patients with X-linked CGD using higher (10 mg/kg) but still not ablative dose of busulfan [17]. For CGD patients

suffering also from inflammatory GI manifestations, conservative local and systemic immune modulating medications such as low or high doses of steroids, azathioprine [18] or monoclonal antibodies to TNF-alpha have been used with varying degree of success [8]. Several studies have also shown resolution of the GI manifestations after BMT [15,16,19-27]. However direct comparison of the outcome of the GI manifestations in CGD patients following the different treatment options are scarce. Here we describe our experience in the management of the GI manifestation of patients with CGD and compare the outcome following conservative therapy or BMT.

Methods

Medical records of all CGD patients managed by the Division of Immunology at the Hospital for Sick Children, Toronto, Ontario, from January 1st 2000 to December 31st 2012 were reviewed. The diagnosis of CGD was established by nitroblue tetrazolium reduction and/or neutrophil oxidative burst index (NOBI) measured by dihydrorhodamine oxidation. Specific gene defects were determined by sequencing. "GI manifestations" were defined as previously described [2] with some modifications. Specifically, GI manifestations included diarrhea (persistent, without an infectious cause; with or without blood in the stool), constipation, prolonged vomiting, obstruction, or fistulas as well as involvement of the esophagus, stomach, or bowel confirmed by endoscopy and/or histopathology. GI obstruction was diagnosed as functional or due to mass effect by ultrasound and or endoscopy. Peri-anal disease included abscesses or fissures, but not hemorrhoids or skin tags. Abdominal pain, hepatic granulomata, hepatic abscesses, and all other GI involvement from proven causes, such as gastroenteritis or infectious colitis (eg, Clostridium difficile) were not considered as "GI manifestations". The age at diagnosis of GI manifestations was defined as the earlier of the following: 1). When GI manifestations appeared; 2). When GI inflammation was confirmed by biopsy performed either at the Hospital for Sick Children or referring hospitals; 3). When specific treatment for GI manifestations was initiated. Length of follow up was calculated from the initial examination at the Hospital for Sick Children until last follow up visit or death. Growth was assessed by plotting patients' age versus weight (in kilograms) on the Center for Disease Control growth charts [http://www.cdc.gov/growthcharts/]. Allogeneic bone marrow or cord blood transplantations, but not gene therapy, were offered to all patients who had HLA-matched family donors and markedly reduced NOBI (<2, where normal control is 32-300). BMT, with >3-5 × 10^8 nucleated cells/kg recipient body weight was performed using myeloablative conditioning with 16 mg/kg Busulfan followed by 200 mg/kg Cyclophosphamide, each divided over 4 days, as previously described [28]. Prednisone and Cyclosporine A (target levels of 100-150) were given for graft versus host disease prophylaxis.

Results are expressed as median and range. Categorical variables were compared using Fisher exact test. The level of statistical significance was set at .05. The Hospital for Sick Children Research Ethics Board approved the study.

Results

During the study period, 11 patients, all males were identified as suffering from CGD. No patient was excluded from the study. As described in Table 1, gene sequencing or family history indicated an X-linked inheritance compatible with *CYBB* mutations in 9 patients. In 2 patients, homozygous mutation in *NCF2* or heterozygous mutation in *NCF1* with markedly reduced NOBI (and absent mutations in other genes) suggested autosomal recessive form of CGD. Patients often presented in the first decade of life. Excluding the 2 patients diagnosed at birth because of prior family history, the median age at presentation was 3.3 years (range: 0.2-6.9 years). Presenting symptoms were often infections typical for CGD such as lymphadenitis due to *Staphylococcus aureus* in 2 patients, pulmonary aspergillus infections in 2 patients, serratia marcescens skin infection in 1 patient and liver abscesses in 2 patients. GI manifestations, including colitis and vomiting, were the presenting features of 3 patients. Excluding the 2 patients identified at birth because of prior family history, patients were diagnosed with CGD at the median age of 3.6 years (range 0.3-31 years). Most patients received prophylactic therapy with trimethoprim/sulfamethoxazole and itraconazole except for 1 patient who elected only to receive trimethoprim/sulfamethoxazole and 2 patients in whom trimethoprim/sulfamethoxazole was substituted with ciprofloxacin. Interferon gamma was used in 3 patients for 0.25 to 4 years. None of the patients suffered from BCG disease (BCG is not a routine vaccine in North America) or tuberculosis.

Patient #	Gene Mutation	Age at presentation (years)	Presenting symptom	Age at Diagnosis of CGD (years)
1	*CYBB* c.1546T>C	0.4	Liver abscess, *Staphylococcus aureus* cervical lymphadenitis	0.5
2	*CYBB* c.906_909delTCAC	0.2	*Staphylococcus aureus*, Cervical lymphadenitis and abscess	0.4
3	*CYBB* c.868C>T	1.4	Liver abscesses + colitis (No pathogen isolated)	1.5
4	*NCF1* (heterozygote) c.75-76delGT	7	Skin infection with *Serratia marcescens*	9.7
5	*NCF2* c.1099C>T	5	Pneumonia (unknown pathogen)	31.4
6	X-linked inheritance#	0	NA*	NA#

7	X-linked inheritance#	0	NA*	NA#
8	*CYBB* c.883_87dupGTGGT	3.3	Axillary lymphadenitis due to *Aspergillus*	3.4
9	*CYBB* c.252G>A	3.2	Persistent vomiting	3.6
10	*CYBB* c.121T>G	6.9	Pulmonary aspergillus, colitis	7
11	X-linked inheritance#	18	Pulmonary aspergillus	18.1
*NA: not applicable as diagnosed at birth due to family history of CGD; #: Suggested because additional family member was diagnosed with X-linked CGD				

Table 1: Gene abnormalities and clinical presentation of patients with CGD.

Inflammatory GI manifestations were reported in all 11 patients prior to diagnosis, at presentation or during follow up (Table 2). Prior to the identification of CGD, an erroneous diagnosis of ulcerative colitis or eosinophilic gastroenteritis was made in 1 patient, each. Among the 11 patients, colitis occurred in 8 patients (72.7%), oral aphthous ulcers in 4 (36.4%), peri-anal fissures/abscesses in 4 (36.4%), constipation in 3 (27.2%), significant lower GI bleeding in 2 (18.2%), vomiting in 1 (9.1%) and spontaneous small bowel perforation in 1 (9.0%). Failure to thrive was recorded in 5 of 11 (45.4%) patients, all 5 suffering from colitis. The GI inflammation was treated with various medications including mesalamine, prolonged systemic steroids, and/or azathioprine as well as addition of metronidazole during exacerbations of colitis (Table 2). The response of patients' GI manifestations to these medications was variable; patient #9 required continued systemic steroids due to frequent exacerbations of his GI disease. Patient #6 was relatively stable with mesalamine and azathioprine while patient #10 responded well and was virtually asymptomatic with alternate day systemic steroids for several years.

Patient #	GI manifestation prior to or at diagnosis	GI manifestation during follow up	Specific GI therapy (length of therapy)
1	Constipation, colitis	None	Hypoallergenic diet
2	None	Oral aphthous ulcers, vomiting and diarrhea	None
3	Colitis	Recurrent colitis, tongue ulcers, intussusceptions.	Mesalamine.
4	Prolonged diarrhea, chronic constipation	Oral aphthous ulcers	None
5	Colitis	Oral aphthous ulcers, colitis relapse, peri-anal abscess	Systemic steroids
6	NA*	Colitis, peri-anal fissure, lower GI bleeding, inflammatory colonic polyps	Systemic steroids (1.2 years), Mesalamine, Azathioprine.
7	NA*	Peri-anal fissure, colitis, constipation	Peri-anal fissure Surgery, stool softeners
8	None	Oral aphthous ulcers	None
9	Vomiting, colitis	Spontaneous small bowel perforation, colonic strictures	Systemic steroids (11.6 years), Mesalamine, Azathioprine, Metronidazole, Gastric feeding tube, Home total parenteral nutrition.
10	Colitis	None	Systemic steroids (4 years), Metronidazole
11	Peri-anal disease	Colitis, lower GI bleeding, recurrent peri-anal fissures	Systemic steroids (0.25 years), Colectomy
*NA: Not applicable as diagnosed at birth due to family history of CGD; FTT: Failure To Thrive; GI: Gastrointestinal; INFg: Interferon-gamma			

Table 2: Gastrointestinal manifestations among patients with CGD.

BMT was performed in 4 of 5 patients who had healthy HLA-matched sibling donors (Table 3). One patient elected not to proceed with transplantation, despite persistent colitis requiring prolonged immune suppressive treatments that possibly contributed to life threatening infections. BMT was performed at median age of 16.5 months (range: 8-52 months) with a median of 4.7 months (range: 4-13 months) after diagnosis of CGD. One patient, who had atrial tachycardia with mild to moderate left ventricular dysfunction at diagnosis, died 5 months after BMT from a cardio-respiratory arrest possibly secondary to infection and/or adrenal insufficiency attributed in part to steroids that he was receiving for graft versus host prophylaxis. The last follow up visit of the remaining 3 patients was at a median of 4.0 years (range 3.2-4.6 years) after BMT. At that time they all stopped immune suppressive medications, had >95% whole blood donor chimerism and normal NOBI. Importantly, all the GI manifestations identified prior to BMT resolved. In contrast, 6 of 7 patients, with a median follow up of 6.9 years (range 3.4-20 years) from diagnosis who did not receive BMT, continued to suffer from GI abnormalities. Hence, GI manifestations among patients who did not receive BMT were significantly (p=0.033) more common than those who received BMT. A detailed comparison of the morbidity among the 3 patients surviving BMT with the morbidity among the 7 patients who did not receive BMT is presented in Table 4. Importantly, among the latter 7 patients, 3 failed to thrive (Figure 1) and 2 required growth hormone therapy.

Patient	Age of BMT (years)	Indications for BMT	Graft versus host disease	Outcome and time after BMT
1	0.7	Severe infections, colitis	No.	Died, 0.4 years.
2	0.7	Severe infections	No.	Alive and well, 3.9 years.
3	2	Severe infections, colitis	Yes. Grade 1-2 skin and liver.	Alive and well, 6.6 years.
8	4.3	Severe infections	No.	Alive and well, 8.3 years.
BMT: Bone Marrow Transplantation				

Table 3: Outcome of bone marrow transplantation for CGD.

Patient	Age at last follow up (years)	GI manifestation at last follow up	GI therapy at Last follow up
2	4	None	None
3	6.6	Tongue ulcers*	None
4	16.1	Constipation	None
5	30.7	Peri-anal disease	None
6	18.1	Colitis	Mesalamine, Azathioprine
7	22.5	Constipation	None
8	8.3	None	None
9	15.2	Colitis	Steroids, Azathioprine, Metronidazole, Mesalamine, Home total parenteral nutrition,
10	19.5	None	None
11	38	Peri-anal disease	None
BMT: Bone Marrow Transplantation; TPN: Total Parenteral Nutrition; *Tongue ulcers began after BMT			

Table 4: Outcome of gastrointestinal (GI) complications among patients with CGD.

Discussion

CGD patients are particularly susceptible to infections and uncontrolled inflammation. In recent years there has also been increasing appreciation of the non-infectious inflammatory GI manifestations associated with CGD [2,14,29-31]. Strikingly, and in contrast to previous reports, we found that all 11 patients with CGD had GI manifestations, a percentage that is higher than the 32.8% of GI abnormalities mentioned in a large retrospective US study [2] or the 48% GI manifestations among CGD patients enrolled into a European registry [31]. Even a recent report from a Greece referral center for patients with primary immune deficiency documented GI manifestation only among 14 of 24 (58.3%) patients with CGD [32]. Moreover, colitis was identified among 72.7% of our patients, compared to 40% of patients in the UK and Ireland CGD Registry [26]. Most of our patients had mutations in *CYBB*, similar to previous reports of patients from North America [2,6], suggesting that the genetic defect was not the cause for the high incidence of GI abnormalities in our group. Similarly, it is unlikely that an unidentified environmental pathogen is responsible for the GI abnormalities in our patients, as symptoms improved following treatments with immune suppressive medications. Other, yet to be identified genes or gene modifiers could play a role in the increased GI manifestations observed in our CGD patients. Future prospective studies from various centers across the world will help clarify the incidence of infectious and non-infectious GI abnormalities among patients with CGD, as recently emphasized in a leading editorial [33].

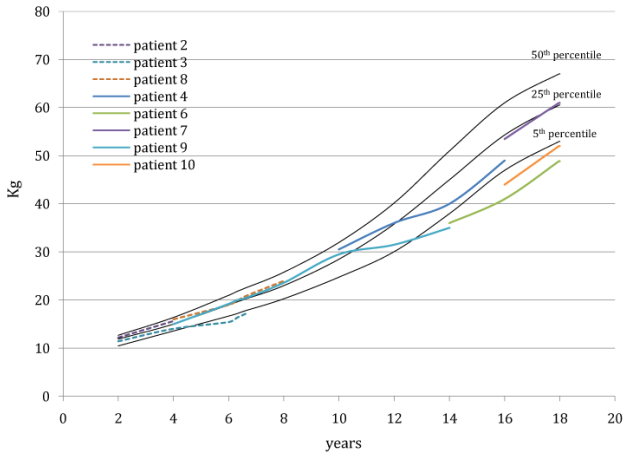

Figure 1: Weight of patients with chronic granulomatous disease. Weight in kilograms (Kg) of patients with chronic granulomatous disease, between 2 and 18 years of age, who received (dashed lines) or did not receive (solid lines) bone marrow transplantations. The 5th, 25th and 50th percentiles (black solid lines) were adapted from the Center for Disease Control growth charts.

Few of our patients were initially misdiagnosed as suffering from colitis or eosinophilic gastroenteritis, particularly when the GI manifestations preceded infections typical for CGD. Because of the frequent GI manifestations, patients are often initially evaluated and managed by care providers, who may not be aware to the possibility of an underlying primary immune deficiency. Moreover, several reports identified patients with abnormal neutrophil superoxide generation as suffering from inflammatory bowel disease [2,7,14,15,34,35]. Clues to the correct diagnosis include the very early age of presentation, which is uncommon among patients with inflammatory bowel disease, the presence of extra-intestinal infections typical of CGD and histological features such as pigmented macrophages and granuloma [7,36,37].

The infectious GI involvement in patients with CGD has significant clinical implications, as 8 of our patients suffered from colitis, 5 failed to thrive, 2 had severe GI bleeds and another had bowel perforation,

emphasizing the potential morbidity from the GI complications. Many patients required prolonged use of immune suppressive medications and 1 patient received systemic steroids for more than 11 years. Importantly, we found that GI complications were significantly more common among patients who did not receive BMT than those who received BMT. Similar to our experience, several case series showed excellent survival of patients with CGD following HLA-matched allogeneic stem cells transplantations [16,19,21,22,24-26,38]. Outcome was particularly favorable when transplantations were performed with an HLA-matched sibling donor and at an early age, although outcome of HLA-matched unrelated donor transplants is reported to be similar [21,27]. In contrast to a recent Swedish report [38], yet similar to the UK and Ireland CGD Registry [26], we did not find significant difference in mortality between patients that did or did not receive BMT, while morbidity was reduced following transplantation. Among our patients, colitis that was present prior to transplantation resolved and none of the patients without colitis pre-BMT developed colitis during 3.2-4.6 years of follow-up, which is similar to previous reports (Table 5) of the overwhelming beneficial effects of hematopoietic stem cell transplantation on colitis [15,16,19-26,38]. Indeed, a recent multicenter study reported that transplantation cured colitis in 22 of 24 patients with CGD, with 1 patient dying after refusing immune suppressive treatment for acute graft versus host disease [27]. Our findings are also concordant with the recent report indicating improved quality of life and emotional well-being in CGD children who received BMT [38] and suggest that BMT should be considered for patients with CGD suffering from severe GI manifestations, particularly if an HLA-matched sibling donor is available.

Number of CGD patients with GI manifestations	Number of CGD patients with colitis	Number of CGD patients with cured colitis and alive.	Length of follow up (years)	Reference
3	3	3 Cured. All alive.	0.7-5	15
6	4	4 cured. All alive.	1-14	16
2	2	2 Cured. All alive.	1.3	19
1	1	1 Cured. All alive.	1	20
11	10	9 cured. 8 alive.	0.8-9.8	21
1	1	1 Cured. All alive.	>2	23
4	1	1 Cured. All alive.	1-8	25
25	24	22 cured. 23 alive.	0.3-9.7	27
4	2	2 Cured. 1 alive.	12	38

Table 5: Effects of hematopoietic stem cell transplantations on colitis in patients with CGD.

In conclusion, we demonstrate here a very high frequency of inflammatory GI abnormalities among patients with CGD, resulting in significant morbidity and life threatening complication, which can be cured by BMT.

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