Gastrointestinal Manifestations of Patients with Chronic Granulomatous Disease

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ABSTRACT

Chronic Granulomatous Disease (CGD) represents a group of inherited disorders of phagocytic system, manifesting recurrent infections at different sites. The present study was accomplished in order to determine the gastrointestinal manifestations of CGD patients.

Fifty-seven patients (38 males and 19 females) with CGD, who had been referred to three immunodeficiency referral centers in Iran, were studied during a 24-year period (1980-2004).

The median age at the time of study was 14.5 years old (1-56 years). The median onset age of symptoms was 5 months (1 month – 13.75 years), and that of diagnostic age was 5 years (2 months- 54.1 years), with a diagnostic delay of 33 months, on average. Seven patients were presented with acute diarrhea, 3 with oral candidiasis, and 2 with liver abscesses as the first chief complaints. Twenty-four cases (42.1%) had been complicated by gastrointestinal manifestations during their course of the disease. Of those, 12 cases (21.1%) had diarrhea, 7 (12.3%) oral candidiasis, 5 (8.8%) hepatitis, 4 (7.0%) hepatic abscess, and 2 cases (3.5%) gastric outlet obstruction. Also, failure to thrive was detected in 6 patients (10.5%). Four patients died (7%).

CGD should be excluded in any patient with gastrointestinal manifestations especially chronic diarrhea, hepatic abscess, and gastric outlet obstruction.

Key words: Chronic granulomatous disease, infection, gastrointestinal disorders, diarrhea

INTRODUCTION

Chronic Granulomatus disease (CGD) is an inherited phagocytic disorder revealing the reduced nicotinamide dinucleotidie phosphate (NADPH) oxidase complex. As a result of the defect in this key host defense pathway, CGD patients suffer from recurrent life-threatening infections by catalase-positive bacteria and fungi.[1-6]

CGD is a rare syndrome, which its prevalence has been already estimated as approximately about 1 per 1,300,000 individuals in population of Japan[7] and Australia.[8] The infectious complications of CGD occur in organs exposed to numerous micro-organisms, namely, the skin, mucous membranes, and gastrointestinal tract, as well as in organs with a large

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population of reticuloendothelial cells, such as the liver, lymph nodes, spleen, and bones.[9] Gastrointestinal tract involvement, observed in the majority of affected individuals, may be present initially and recurrently, mimics other entities such as inflammatory bowel disease, and causes substantive morbidity and mortality. Disorders of motility, ulceration, obstruction, and infection (e.g., abscesses) occur from the mouth to the anus and stereotypically manifest with vomiting, diarrhea, abdominal pain, weight loss, and fever.[9]

Since the initial clinical description of CGD in 1957,[1] a large number of clinical reports have been published about the disorder. However, most of these have merely focused on specific clinical issues, such as the occurrence of unusual or rare infections, non-infectious complications, or therapy, and have involved limited numbers of patients. There have been relatively few original reports involving comprehensive clinical studies in large numbers of patients.[10]

Because CGD is relatively uncommon, it has previously been difficult to develop a detailed and comprehensive clinical picture of the disorder. Accordingly, a national registry of patients with primary immunodeficiency (PID) including CGD has recently been established in Iran since 1999 in order to characterize epidemiological and gastrointestinal manifestations of these patients.[11] According to this registry, CGD following Common variable immunodeficiency is the second most common PID in Iran, consisting about %20 of these groups of patients.[11]

MATERIALS AND METHODS

In order to determine the gastrointestinal manifestations of CGD, 57 patients with CGD were investigated, who had been referred to Children's Medical Center, Maseeh Daneshvari Hospital, and Rasoul Akram Hospital, the three most important immunodeficiency referral centers in Tehran, Iran. These data have been gathered by interviewing the patients and reviewing their medical documents during a period of 24 years (1980-2004).

The diagnosis of CGD was made according to the standard criteria, including a negative quantitative nitro blue tetrazolium (NBT) test and total failure of chemiluminescense after phagocytosis. Patients were considered to have CGD if they had at least one test indicating abnormal function in the phagocytic NADPH oxidase system or abnormal intracellular bactericidal activity of their phagocytic cells.[3-6]

A four-page questionnaire was developed to contain all the patient's demographic information, first clinical presentation, age at the time of onset of symptoms, age at the time of diagnosis of CGD, basic immunological laboratory tests, and follow-up information including the gastrointestinal manifestations in the course of the illness. This questionnaire was filled by the expert physicians of the hospitals participating in this project.

Univariate analysis was accomplished, using SPSS statistical software package (version 10.0).

RESULTS

Fifty-seven CGD patients (38 males and 19 females) with the age range of 1-56 years (median 14.5 years) were reviewed from 1980 to 2004. These patients were members of 47 families and the parents of 43 patients (75.4%) were consanguineous. The median age at the onset of symptoms was 5 months of age (1-165 months). Twenty-nine out of 57 patients (50.9%) showed symptoms by the age of 5 months, while 14 patients (24.6%) did not show symptoms until after the age of 2 years old (Figure 1).

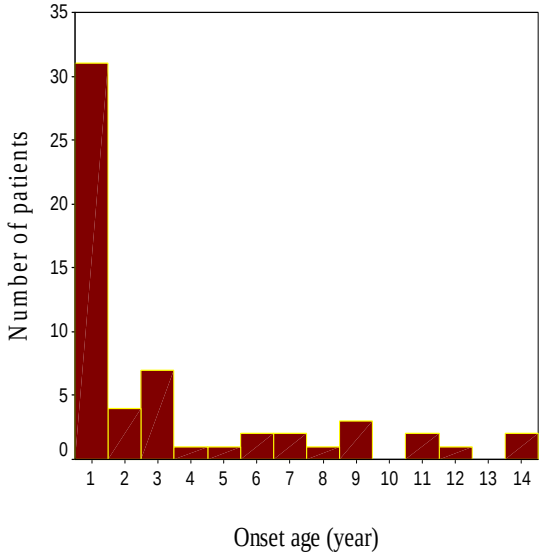

Figure 1. Onset age of symptoms in 57 patients with chronic granulomatous disease.

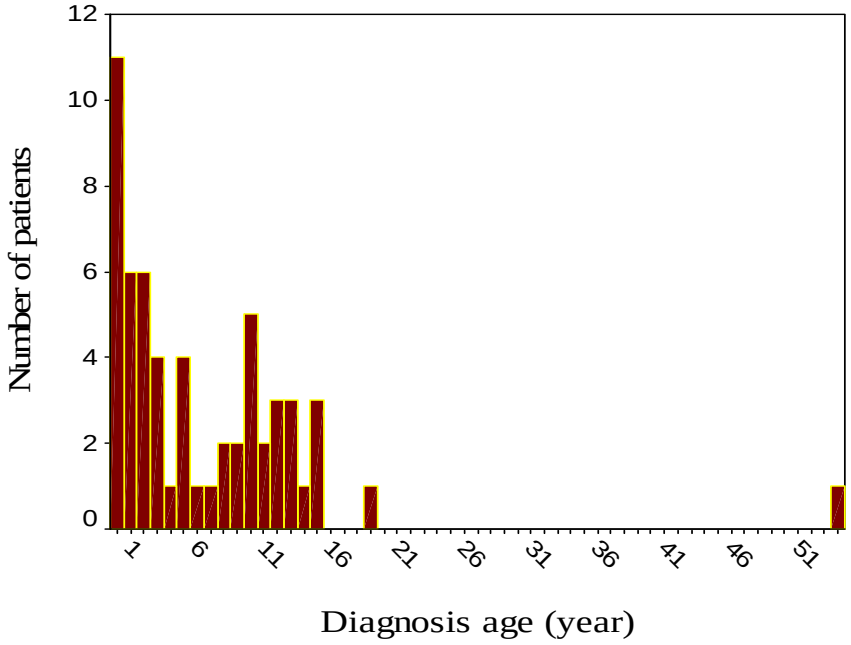

Figure 2. Diagnostic age of 57 patients with chronic granulomatous disease.

The median diagnostic age was 5 years (2 months-54.1 years), with a diagnosis delay of 33 (1-485) months, on average (Figure 2).

At present, 47 patients are followed biannually. Four patients died (7%). The remaining 6 patients could not be localized since more than one year ago.

Lymphadenopathy, pulmonary and skin infections were the most common manifestations of CGD, followed by gastrointestinal, upper respiratory tract, skeletal and central nervous system involvement.

Seven patients were presented with acute diarrhea, 3 with oral candidiasis, and 2 with liver abscesses as the first chief complaints. Twenty-four cases (42.1%) had been complicated with gastrointestinal manifestations during their disease. Of those, 12 cases (21.1%) had acute infectious diarrhea, 7 (12.3%) oral candidiasis, 5 (8.8%) hepatitis, 4 (7.0%) hepatic abscess, and 2 cases (3.5%) gastric outlet obstruction. Salmonella were detected as the cause of acute diarrhea in 3 patients. Also, failure to thrive was noticed in 6 patients (10.5%).

DISCUSSION

CGD is a rare condition known to be associated with repeated and life threatening bacterial and fungal infections in multiple sites such as lymph nodes, gastro intestine, bones, and lungs. In this study the gastrointestinal manifestations of 57 cases, referred to our centers during a 24-year period, were reviewed.

The gastrointestinal manifestations of CGD are diverse, include anatomic and functional abnormalities, and are characterized pathologically by abscesses and granulomas containing lipid-filled histiocytes.[12,13] CGD is associated with recurrent pyogenic abscess formation in regional lymph nodes, pulmonary parenchyma, and liver which requiring surgical drainage.[14] Liver abscess was detected in 7% of our cases, which was lower than the previous study by Winkelstein JA et al.[10] Hepatic abscesses are frequent complications of CGD.[9] National Institutes of Health has reported 22 patients with hepatic abscesses in 156 CGD cases.[15] Also, 98 patients with liver abscesses had been detected in the CGD registry embracing information on 368 cases from 77 different medical institutions[10] and 69 patients in another multi-institution review on 168 CGD cases.[6] These considerable differences in our data compared with other large series may be due to lack of awareness about this rare immunodeficiency and its complications among the general practitioners in our country.

In addition to infections, a variety of disorders have been described in patients with CGD for which no infectious etiology has been identified.[10] These have included obstructive lesions of the gastrointestinal tract.[10,16,17] Gastric outlet obstruction was seen in 2 cases entered in our database. The most common gastric complications of CGD were vomiting, weight loss, and epigastric pain related to gastric outlet obstruction.[9] Intestinal manifestations of our CGD patients included diarrhea, which was seen in 12 patients. Although Salmonella was the cause of acute diarrhea in 3 patients, it is the most common and virulent pathogen, accounting for 33% of infections.[18]

At present there is no treatment for the underlying defect in the phagocyte respiratory burst. Attempts have been made to restore active oxygen metabolites to the CGD neutrophil but it has not been very successful, and aggressive treatment of infections remains the mainstay of patient management. The pathogen involved and its sensitivity must be identified and the appropriate antimicrobial drug administered.[19] A multifaceted therapeutic approach has been responsible for the greatly improved prognosis in CGD. The key elements of the current therapy include the following: avoidance of certain sources of pathogens, use of prophylactic trimethoprim-sulfamethoxazole or dicloxacillin, early use of parenteral antibiotics including antifungal drugs, surgical drainage or resection of rectal infections, granulocyte transfusions for poorly responding infections, and the use of prophylactic recombinant human interferon gamma. Moreover because CGD results from a defect in hematopoietic stem cells, bone marrow transplantation is a rational option to establish a stable population of normal myeloid progenitors.[2] Thus, the prognosis for patients with CGD appears to be better than envisioned when the disorder was originally described. The data presented here provide clear evidence that although CGD still claims the lives of children and young adults at unacceptable rates, it is a disease with a finite spectrum of clinical presentations that can be anticipated and managed. With this clearer picture of CGD, new prophylactic and therapeutic approaches that address the ongoing infections and inflammatory complications of this disease can be pursued.[10]

Careful physical examination, in concert with appropriate diagnostic studies, is necessary to delineate intraabdominal pathologic processes. Abdominal radiographs, ultrasonography, computerized tomography, and endoscopy are useful ancillary diagnostic procedures. Drainage of accessible abscesses, antimicrobial therapy based on organisms cultured from blood and tissue, and interferon gamma may lead to suppression or eradication of infections and resolution of symptoms. Corticosteroids are useful for gastric outlet obstruction and sulfasalazine and cyclosporine for large bowel disease.[9]

Early diagnosis of the disease is crucial. With early diagnosis and prompt institution of appropriate therapy, the mean surviving age of CGD patients will be increased.[20] In view of the possibility of timely treatment, infection prophylaxis, CGD should be excluded in any patient with gastrointestinal manifestations especially chronic diarrhea, hepatic abscess, and gastric outlet obstruction. Further studies are necessary to optimize the prevention and treatment of gastrointestinal tract disease in CGD patients.

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