Chronic Granulomatous Disease: A Clinical Survey of 41 Patients from the Iranian Primary Immunodeficiency Registry

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\textbf{Key Words}
Bacillus Calmette-Guérin · Chronic granulomatous disease · Infection · Iran · Lymphadenopathy

\textbf{Abstract}

\textbf{Background:} Chronic granulomatous disease (CGD) represents a group of inherited disorders of the phagocytic system, involving recurrent infections at different sites, especially the respiratory system. The present study was accomplished in order to determine the clinical spectrum of Iranian patients with CGD. \textbf{Methods:} Forty-one patients (29 males and 12 females) with CGD, who had already been referred to two immunodeficiency referral centers in Iran, were reviewed during a 22-year period (1980–2002). \textbf{Results:} These patients belonged to 34 families, and 56\% of them were consanguineous. The median age at the time of study was 12 years (3 months to 22 years). The median age at onset of symptoms was 4 months (1 month to 12 years), and the median diagnostic age was 5.5 years (2 months to 20 years), with a diagnostic delay of 3 years on average. The most common presenting complaint in our CGD patients was lymphadenopathy (seen in 11 patients, 26.8\%). The most common manifestations of CGD (in descending order) were lymphadenopathy (75.6\%), pulmonary infections (65.9\%) and skin involvement (63.4\%) during their illness, followed by gastrointestinal (56.1\%), skeletal (29.3\%), upper respiratory tract (26.8\%) and central nervous system (2.4\%) involvement. \textbf{Conclusions:} Early diagnosis of the disease is crucial. In view of the possibility of timely treatment, i.e. prophylactic treatment of infection, CGD should be excluded in any patient with unexplained infections or granulomas.

\textbf{Introduction}

Chronic granulomatous disease (CGD) is a rare phagocytic disorder involving the reduced nicotinamide dinucleotide phosphate (NADPH) oxidase complex that results in defective superoxide generation in which phagocytic cells are unable to kill certain bacteria and fungi after ingesting them [1–8].
Clinically, CGD is characterized by recurrent life-threatening infections and excessive granuloma formation, most typically as pneumonia, infectious dermatitis, and recurrent or severe abscess formation beneath the skin and in the organs of the reticuloendothelial system [2, 6].

Over the past 10 years, the membrane-bound and cytoplasmic components of the phagocyte NADPH oxidase have been identified, cloned, and sequenced and their mechanisms of assembly into a functional enzyme complex have been characterized. CGD is a genetically heterogeneous disease caused by mutations in any of the four structural components of NADPH oxidase, including the membrane-bound glycoprotein gp91phox (phagocyte oxidase) and p22phox and the cytoplasmic components p47phox and p67phox [8, 9].

Since the initial clinical description of CGD in 1957 [1] and the delineation of its underlying defect in intracellular phagocytic microbicidal activity in 1967 [7], a large number of clinical reports have been published about the disorder. However, most of these have already 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 patient cohorts [10].

The prevalence of CGD has already been estimated as approximately about 1 per 1,200,000 individuals [8, 10], and due to the paucity of the cases it has been difficult to develop a detailed and comprehensive clinical picture of the disorder. Accordingly, a national registry of patients with primary immunodeficiency including CGD has already been established in Iran since 1999 in order to characterize epidemiological and clinical features of these patients [11]. Due to this registry, CGD following common variable immunodeficiency is the second most common primary immunodeficiency in Iran, comprising about 20% of these patients [11].

**Patients and Methods**

In order to determine the clinical features of CGD, patient records of 41 patients with CGD were reviewed, who had been referred to the Children’s Medical Center and the Masih Daneshvari Hospital, the two most important immunodeficiency referral centers in Iran. These data have been gathered by interviewing the patient himself and reviewing his/her medical documents during a 22-year period (1980–2002).

The diagnosis of CGD was made according to standard criteria, including compatible clinical history, a negative quantitative nitroblue tetrazolium test and total failure of chemiluminescence after phagocytosis. Patients were considered to have CGD if they had at least one test indicating abnormal function of the phagocytic NADPH oxidase system or abnormal intracellular bacterial activity of their phagocytic cells [3–8].

Forty-five patients met the above-mentioned criteria, and of these, 41 cases that were followed up and had adequate medical records were enrolled in this study. All of them were alive at the time of diagnosis.

Data analysis was accomplished using the SPSS statistical software package (version 10.0).

**Results**

**Characteristics of the Patients**

Forty-one CGD patients (29 males and 12 females) aged 3 months to 22 years (median 12 years) were reviewed from 1980 to 2002. These patients belonged to 34 families, and the parents of 23 patients (56.1%) were consanguineous. The median age at the onset of symptoms was 4 months (1–144 months). Eighteen out of 41 patients (43.9%) showed symptoms by the age of 3 months, and 27 patients (65.9%) by the age of 1 year. Twelve patients (29.3%) did not have symptoms until after the age of 2 years. The median diagnostic age was 5.5 years (2 months to 20 years; mean = 6.34 ± 5.59 years), with a diagnostic delay of 3 years (range: 0–12, mean = 3.88 ± 3.81 years) on average (fig. 1).

At present, 31 of these 41 patients are followed biannually. Five patients have died (12.2%) during the follow-up because of recurrent infections and complications, including sepsis after pneumonia (a 4-year-old boy), lung abscesses (a 6-year-old boy), bronchiectasis (a 13-year-old boy), hydatid cyst of the lung (a 11-year-old boy) and meningitis with *Escherichia coli* (a 3-month-old girl). The remaining 5 patients could not be localized since they died more than 1 year before the study enrolment at the ages of 3, 4, , 17, and 19 years, respectively.

**Presenting Symptoms**

The most common presenting complaint in CGD patients was lymphadenopathy, detected in 11 patients (26.8%). Other presenting manifestations in descending order of frequency were: skin abscesses (9 patients, 21.9%), bacterial pneumonia (5 patients, 12.2%), dermatitis (4 patients, 9.8%), septic arthritis, diarrhea, and Bacillus Calmette-Guérin (BCG)osis (each of them in 3 patients, 7.3%). Also, 1 patient presented with purpuric lesions and another one with osteomyelitis. It is considerable that only 1 patient had been diagnosed before the onset of clinical complications based on familial history and screening with a nitroblue tetrazolium test.
**Clinical Features**

Lymphadenopathy, and pulmonary and skin infections were the most common manifestations of CGD, followed by gastrointestinal, upper respiratory tract, skeletal and central nervous system involvement (fig. 2).

Lymphadenopathy was reported in 31 of the 41 patients (75.6%) during their illness. In 7 patients, CGD was complicated by BCGosis as a generalized lymphadenopathy after BCG vaccination.

Twenty-seven of the 41 patients (65.9%) developed pulmonary involvement at some periods during the course of their illness. Twenty of them (48.7%) had pneumonia as the most common pulmonary complication. Thirteen patients (31.7%) had lung tuberculosis, which was definitely diagnosed in a positive sputum smear test, and in 7 it was complicated by BCGosis following tuberculosis vaccine inoculation. Pulmonary aspergillosis with *Aspergillus fumigatus* was seen in 4 patients (9.7%), who...
were diagnosed by lung biopsy and positive culture. Moreover, 3 patients (7.3%) presented with a pulmonary abscess and 1 with a hydatid cyst. One CGD patient had also suffered from bronchiectasis during the course of illness, and diagnosis was based on clinical symptoms, chest X-ray, and high-resolution computed tomography. He died 1 year after the diagnosis was made. Two patients had tuberculosis and aspergillosis together, and combined tuberculosis and pulmonary abscess was also detected in 3 patients.

Skin involvement was seen in 26 patients (63.4%), including subcutaneous abscess (22 cases, 53.7%), cellulitis (12 cases, 29.3%) and skin fistula (3 cases, 7.3%).

Twenty-three cases (56.1%) had gastrointestinal disorders as complications. Of those, 11 cases (26.8%) had chronic diarrhea, 7 (17.1%) oral candidiasis, 5 (12.2%) hepatitis, 4 (9.8%) hepatic abscess and 2 cases (4.9%) gastric outlet obstruction. Also, failure to thrive was detected in 6 patients (14.6%). Twelve cases had bone and joint infections (29.3%), including osteomyelitis in 9 patients (21.9%), and septic arthritis in 8 patients (19.5%).

Upper respiratory tract involvement was demonstrated in 11 patients (26.8%), including otitis media (10 cases, 24.4%), acute sinusitis (5 cases, 12.2%) and mastoiditis (1 case, 2.4%). One patient had also mucormycosis.

Only 1 patient had central nervous system involvement and died because of brain abscess and meningitis caused by *E. coli* (2.4%). None of the patients developed a malignancy.

Unfortunately, the standard microbiologic data about microorganisms responsible for the infections at the various sites were not available. Apparently, the appropriate culture examinations for the detection of organisms at the various organs have not been performed before empiric therapy in almost all of the patients.

**Discussion**

CGD is a rare condition known to be associated with repeated and life-threatening bacterial and fungal infections at multiple sites, e.g. lymph nodes, gastrointestinal tract and lungs [8, 10]. This report was the first on Iranian CGD patients, comprising the clinical data of 41 patients who had been treated and evaluated in our centers during a 22-year period.

Male patients constituted more than two thirds of our patient group (70.7%), which is in agreement with previous studies [10, 12–14]. CGD may be inherited as an X-linked or autosomal recessive disorder, of which X-linked CGD accounts for about 70% of all CGD patients [15]. The male to female ratio in our study (2.4/1) and in a Tunisian study (1.8/1) [13] was lower than in other studies [10, 12, 14], which may be due to the higher autosomal recessive inheritance due to the increased consanguinity of families in Iran (56.1%) and Tunisia (75%) [13]. However, a more accurate description of hereditary patterns needs a precise determination of the patients’ genotype, which is not feasible due to poor facilities in our country.

Most patients were alive when they were entered into the registry, and most of the living patients were in their 1st or 2nd decade of life when entered into the registry. In the present series, 12.2% of the patients were either dead at the time they were registered or died during the follow-up period. The original designation of CGD was ‘fatal granulomatous disease of childhood’ [1], and of the first 92 patients reported in the literature, 45 died of the disease [16]. Fortunately, the prognosis of patients with CGD appears to have improved significantly since its original description [17–19]. The current mortality rate is 2–5% per year [10]. There may have been some bias with respect to either under- or underreporting of patients who had deceased at the time they were entered into the registry.

Most CGD patients have at least one unusual or severe infection during the 1st year of life, and more than 70% are identified by unusual susceptibility to serious infections before their 2nd birthday. These data are in accord with previous studies [6, 13, 20]. Patients affected by the classic form of CGD will begin to develop infections early in lifetime, even within the 1st week, but usually during the 1st year [21]. Although the newborn with CGD receives antibodies from its mother, the phagocytes are its own. Thus he is in jeopardy of infections from the first moments of birth [6].

The mean diagnostic age was 6.34 years, with a diagnostic delay of 3.88 years, which was higher than in a previous study of 77 different institutes [10]. Although half of the patients with CGD (51.2%) were diagnosed before the age of 5 years, a significant number (19.5%) were not diagnosed until the 2nd decade of their life. The average diagnostic delay was 3.9 years in our patients. In a study by Finn et al. [22], in London, the mean diagnostic delay was 1.5 years in the 1980s in comparison with 4.6 years in the 1960s. This long diagnostic delay may be due to the insidious and unspecific symptoms of the disease, which do not attract the attention of the practitioners, even if the patient presents with complications or symptoms for several times or has a sibling which has been diagnosed.
before. These data show the lack of awareness of CGD among the general practitioners and pediatricians in our country.

Lymphadenopathy was the most common presentation (75.6%), and BCGosis, a generalized lymphadenopathy following tuberculosis vaccine inoculation, occurred in 22.6% of these patients, which was similar to the percentages of previous studies [23, 24]. Furthermore, the unusual reaction to BCG was the initial clue in 3 cases with suspected CGD. Previously, adverse reactions to BCG have been well documented in these patients [25, 26]; consequently, BCG vaccination should be avoided in CGD patients.

The pulmonary system is the second site of infection in our study. In some other studies, respiratory manifestations have already been stated to be the most common ones [10, 13, 20, 27]. Thus, it is obvious that respiratory manifestations are common in CGD patients. The respiratory involvement, as the first manifestation, occurred only in 5 cases (12.2%). Thus it is interesting that although respiratory involvement is common during their lifetime, it is unusual as the first manifestation. Pneumonia was the most common complication, seen in 48.7% of our patients. This is probably because of the easy exposure of the organ to external pathogens such as bacteria, fungi and viruses. Some other studies have also shown that pneumonia has been the most common complication [5, 6, 10, 16, 18, 20, 21] while in one series skin infections were the most prevalent [17]. However, in each of these series, suppurative adenitis, rather than abscesses, was the second most prevalent infection. The differences in the relative prevalence of infections between the present and previous series may relate to a variety of factors, including the number of patients reported, the changing clinical expression of the disorder over time, and the way in which information on specific infections was requested and/or reported [10]. We reported only 1 case with bronchiectasis during the course of illness; however, we did not screen our patients for bronchiectasis and did not perform high-resolution computed tomography in all of them, so the number of patients with bronchiectasis may be underestimated in our study.

In our patient cohort, pulmonary tuberculosis was the second common respiratory involvement (31.7%). Although Lau et al. [25], in Hong Kong, had reported a case of CGD with pulmonary tuberculosis, this infection did not play a significant role among the CGD patient infections according to other studies [18, 20]. The latest estimated incidence of smear-positive tuberculosis in Iran was 24 in a population of 100,000, and the estimated number of patients with smear-positive pulmonary tuberculosis was 16,889 [28]. Although, the high prevalence of pulmonary infection with tuberculosis could be due to the high incidence of tuberculosis and the high exposure to Mycobacterium tuberculosis in our country, it seems that CGD patients might be susceptible to tuberculosis infections, and special attention to and appropriate prevention of tuberculosis should be suggested in all of them.

In cases with CGD, several episodes of aspergillus pneumonia may occur, and effective immunity to the organism does not develop after infection [29]. Nearly 10% of the total 41 patients already had aspergillus pneumonia in our study, which is similar to previous series of patients with CGD [16, 29]. However, in a more recent series, the frequency of aspergillus infection was higher than that of other series of CGD patients [10, 18, 30, 31]. As a result of the improvement in controlling bacterial infections due to antibiotic prophylaxis and treatment, invasive fungal infections, especially the ones of aspergillus species, are now the most important causes of morbidity and mortality in CGD [8, 29].

CGD is associated with recurrent pyogenic abscess formation in regional lymph nodes, pulmonary parenchyma and surgical drainage of the liver [32]. Lung abscess was detected in 7.3% of our cases, which was lower than in the study by Winkelstein et al. [10]. All of the patients with pulmonary abscess had been infected with tuberculosis, and 1 of them had a history of aspergillus infection. Also, 22 of our patients (53.7%) manifested skin abscesses during the course of their disease, which was higher than in a previous study [10]. Moreover, liver abscesses was detected in 9.8% of our patients (4 in 41). On the other hand, the National Institutes of Health have reported on 22 patients with hepatic abscesses in 156 CGD cases [33]. Also, 98 patients with liver abscesses have been detected in the CGD registry containing 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 the lack of awareness of this rare immunodeficiency and its complications among the general surgeons in our country.

Although more than 20% of our patients also experienced osteomyelitis, which was similar to a previous study, the frequency of cellulitis in our study was increased compared to a previous series [10].

In addition to infections, a variety of disorders have been described in patients with CGD for which no infectious etiology has been identified [10], e.g. obstructive lesions of the gastrointestinal tract [10, 34, 35]. Gastric...
outlet obstruction was seen in 2 cases of our database. None of the patients developed a malignancy, which was in agreement with a previous study [10].

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 have not been so successful, and aggressive treatment of infections remains the mainstay of patient management. The pathogen involved and its sensitivity must be identified to determine the appropriate antimicrobial drug for effective treatment [21]. 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, early use of antifungal drugs, surgical drainage or debridement when feasible, granulocyte transfusions for poorly responding infections, and the use of prophylactic recombinant human interferon-γ [8, 10, 36–38]. Prophylactic antibiotics and interferon-γ have reduced bacterial infections, but there is also the danger of life-threatening fungal infections which are not altered by trimethoprim-sulfamethoxazole prophylaxis [36]. Itraconazole appears to be an effective and well-tolerated prophylaxis that reduces the frequency of fungal infections in CGD [39]. Gene therapy and bone marrow transplantation trials in CGD patients are ongoing and show great promise [8].

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 infectious and inflammatory complications of this disease can be pursued [10].

Early diagnosis of the disease is crucial. With early diagnosis and prompt institution of appropriate therapy, the mean age of CGD patients will be increased. In view of the possibility of timely treatment (infection prophylaxis), CGD should be excluded in any patient with unexplained infections or granulomas [40].

It seems necessary for future studies to take the genotype of our CGD patient registry into consideration. Furthermore, carrier screening of X-linked cases in certain families could be beneficial to early diagnosis and prevention of severe complications.

Acknowledgment

We are grateful to Drs. L. Atarod, A. Ahmadi Afshtar, N. Bazargan, Z. ChavoshZadeh, M. HaydarZadeh, M. Nabavi and M.H. Bemanian, who assisted us at every step of this project. We gratefully acknowledge the efforts of Dr. H. AbdollahPour, K. Abolmaali, L. Amiri Kordestani, J. Bakhshaei, Sh. Faeri Razi, Z. Habibi, T. Hojati Ashrafi, M. Mahmoudi, M. Nikzad, F. Rafiee Samani, A. Shirani and M. Yaziri for their role in collecting the data. We also thank the laboratory personnel, Mrs. A. Isaeian, L. Nikfarjam and A. Azimdoust, and our secretarial personnel, Mrs. M. Andali, Ms. H. Eghdami, Mrs. Sh. Ekrami, Ms. N. Hasani, and Ms. Z. Shobayri, for their arrangements and administrative efforts.

References

Chronic Granulomatous Disease in Iran


