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Clinical and Radiological Aspects of Chronic Granulomatous Disease in Children: A case Series from Iran

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ABSTRACT

Chronic granulomatous disease (CGD) is a rare disorder of phagocytes, predisposes patients to bacterial and fungal infections. The main purpose of this study was to determine the clinical, radiological, pathologicial features, outcome and response to treatment of children with CGD. Thirteen patients with CGD, who had been referred to National Research Institute of Tuberculosis and Lung Disease (NRITLD), were reviewed during a 6 year period (1999-2005). There were 10 (76%) male and 3(24%) female cases. The median age of the patients was 9 years (1 month-12 years).Family history of CGD was reported by 7 patients. The median diagnostic age was 8 years, with a diagnostic delay of 4.5 years. The most common manifestations of CGD were pulmonary infections and skin involvement, followed by generalized lymphadenopathy. The most common radiological findings were multiple lymphadenopathy in mediastinal region and fibrotic changes in lung fields. Two patients died of pulmonary infections. Based on the results of this research, immunologic evaluations especially evaluation for CGD is highly recommended in children suffering from recurrent pulmonary infections, cutaneous or hepatic abscesses, or infections caused by uncommon pathogens. Early diagnosis and prophylactic treatment both, prevent further development of the lesions, irreversible complications and decreasing mortality and morbidity rates in children suffering from CGD.

Key word: Chronic granulomatous disease; Children; Infection; Radiology

INTRODUCTION

Chronic Granulomatous Disease (CGD) is a rare inherited disorder in which antimicrobial activity of phogocytes is impaired due to the lack of reactive oxygen species, or oxidative burst, produced by NADPH oxidase.[1-9]

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The hallmark of this genetic disorder (X-Linked or AR) is the occurrence of purulent inflammation due to low-grade microorganism.[1-3] Although many organs may be involved with infection, the most common sites are lung and skin. The annual incidence of CGD is estimated to be 1 in 200,000-250,000 live births.[5]

Many patients are diagnosed in the first year of life but there are some reports of late onset of CGD.[3,4,10] According to a study in Iran, the median age at onset of symptoms is 4 months, and the median diagnostic age is 5.5 years.[8]

The aim of this research was to describe the clinical, radiological, laboratory and evolution characteristics of 13 patients with CGD admitted in Pediatric Ward of NRITLD.

PATIENTS AND METHODS

In this descriptive case-series study, clinical, laboratory, and radiological data were obtained from the medical records of all patients with chronic granulomatous disease admitted in the pediatric ward at NRITLD, a referral center for tuberculosis and lung diseases, from 1999-2004. Thirteen patients were found to have CGD, with the pediatric age ranging between 3-15 years.

RESULTS

In this research the collected data of 13 patients were evaluated and analyzed. There were 10 (76%) male and 3 (24%) female cases. Mean age was 9.5±4.7 (median=7.8, range=12) years. These patients belonged to 11 families; Positive family history was detected in 7 (53%) and parents of 4 patients were relatives.

The mean age of onset of symptoms was 2 years (1 month-12 years). In 5 patients (38.4%) the first symptom appeared before 3 months. Also in another 3, no symptom was detected until 2 years of age. In a single 12-year old male case, drug resistant pneumonia was found as the first manifestation of the disease.

The mean age of diagnosis of disease was 8±4.3 (Median=6.4, range=11) years, and mean time duration between the onset of first symptom and diagnosis of disease was 4.5±2.1 (Median=3.6, range=6) years. In 12 patients the growth curve was below 5%, while in one case this curve was 10%. Figure 1 shows the frequency clinical manifestations.

In 3 patients with osteomyelitis, 2 showed rib involvement while in 1 case the scapula was affected.

Aspergillus fumigatus was detected in pulmonary secretion of 5 patients suffering from pneumonia as well as in the biopsied material obtained from rib of 1 patient.

The radiological (Chest X-Ray) and CT-Scan manifestations are presented in table 1.

Regarding the laboratory findings, NBT (Nitroblautetrazolium) test was less than 5% in 3 (1 male, 2 females) while in rest of the cases it was 0%. Normochromic, normocytic anemia and leukocytosis were reported in all of the patients.

Figure 2 demonstrates the surgical procedures performed on the patients. Based on pathology reports, a granulomatous lesion was found in all of the cases.

In this study, 2 patients (a single 14-year old boy and a single 11-year old girl) expired as a result of drug resistant pneumonia. In the remaining 11 cases, prophylactic regimen (Itraconazole and Cotrimoxazol) was administrated and patients are being followed up.

Table 1. The radiological (Chest X-Ray) and CT-Scan manifestations.

Clinical manifestation	No. of cases
Multiple pulmonary lymphadenopathies	5 cases
Pulmonary fibrotic changes	2 cases
Pulmonary infiltration	2 cases
Rib involvement	2 cases

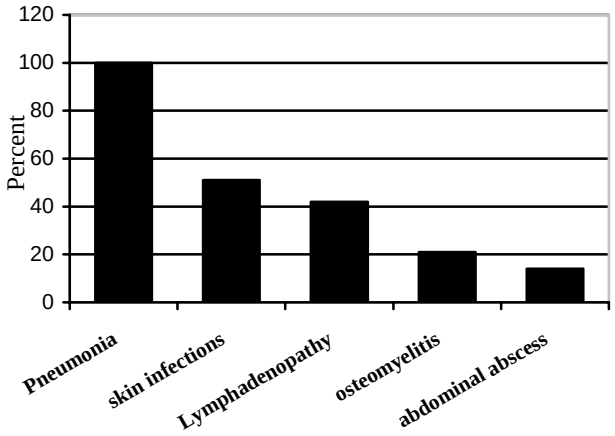

Figure 1. Frequency of clinical manifestation.

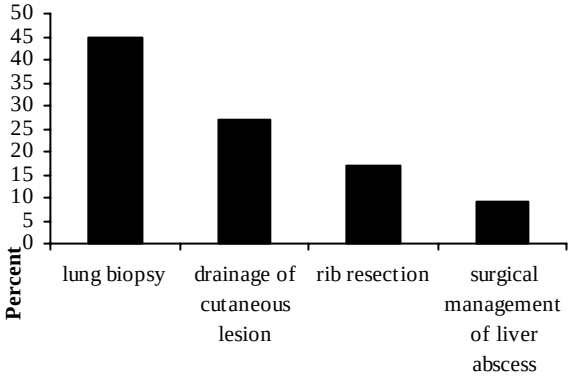

Figure 2. Frequency of surgical procedures performed

DISCUSSION

CGD is a disease that is transmitted genetically by X-linked and autosomal recessive form.[1-9] X-linked form of disease includes about 70% of the patients.[1-3,6] In this research the male population included 2/3 (76%) of the total population which would include the genetic transmission (X-linked) in this group. Since not all of the female patients are AR, evaluation of the patients genotype is not possible without genetic investigations.[2,3,6]

Different studies have shown that 70% of patients are affected with at least one infection before 2-years of age. Similarly as demonstrated in our research 77% of the patients displayed serious clinical manifestations before 2-years of age.[1,2,5,10,11]

In neonates with CGD despite the transmission of maternal antibodies, the phagocytic system of the patient remain disturbed and newborns face various acute infections in the first few months of life.[1-7,10,11] Regarding the result of this research 38% of the patients acquired their first serious infection before 3 months of life.

The diagnosis of CGD is delayed due to multiple features of the infections.[2,4,5]

The mean diagnosis age in this research was 8.5 years and delay in diagnosis was 4.5 years. In a study conducted by Finn et al. in England delay in diagnosis for the years 1960 and 1980 were reported as 4.6 years and 1.5 year respectively.[10] In another investigation performed on 41 patients in Iran, delay in diagnosis was 3.8 years.[11] By comparing our study with the above-mentioned studies, it is easily deduced that there is a large difference between the diagnosis delay of our country and that of developed countries; a fact that requires more attention.[8,9,11]

Winkelstein and co-workers performed a study on 368 patients in U.S.A.[6] According to their results, pneumonia was the most common clinical manifestation and also cutaneous infections and lymphadenopathy were observed in more than 50% of the patients. Comparably, 100% of our patients reported recurrent episodes of pneumonia that were resistant to treatment. Cutaneous infections and lymphadenopathy were also recounted as 52% and 48% respectively.

However other researches reported different results.[3,12] In one investigation by Johnston the clinical manifestations in the patients consisted of adenopathy, pneumonia and skin infections.[3] According to these findings, CGD should be considered in each of above-mentioned manifestations.[9,11]

In our study, Aspergillus was detected in the pulmonary secretions of 38% of the patients; this rate being 10-41% in other studies.[11-13] Among CGD patients with history of pneumonia, more than 40% suffered also from Aspergillus pneumonia at least once.[6,13-15] Moreover in 3 patients with Aspergillus pneumonia, bone involvement was demonstrated, showing the high inclination of this fungus for infecting the bone.[1,2,3,6] In two cases rib resection were performed. Fungal osteomyelitis should be regarded in patients suffering from Aspergillus pneumonia.[1,15]

In spite of relatively high mortality rate in CGD, most of our patients are alive (84%), and two expired due to drug resistance pneumonia. Since our study was conducted only among children, these results cannot be generalized.[1-6]

Results of Winkelstein's study suggest that, in addition to the age of onset of symptoms and age at diagnosis, there are significant differences in the clinical features of CGD between patients with the X-linked and autosomal recessive form of the disease.[6] Moreover genetic laboratory tests for pre-birth diagnosis in carriers decrease the prevalence and it increases the longevity of children.[1,6]

The aim of this research was to evaluate common clinical, radiological and laboratory findings along with the treatment response in CGD patients. It is highly recommended to have full and complete evaluation of the immunological system, especially in CGD, and in children that suffer from recurrent episodes of respiratory and cutaneous infections with uncommon pathogens.[6,8,9,11] Early diagnosis, antibiotic prophylaxis and anti fungal medications (Itraconazole) will decrease mortality and morbidity in these patients.[1-3,8,9,16]

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