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

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Abstract

Background: Chronic granulomatous disease (CGD) is a rare disorder of phagocytes in which absence of superoxide and hydrogen peroxide production in phagocytes predisposes patients to bacterial and fungal infections. The annual incidence of CGD is estimated to be 1 in 200,000-250,000 live births. **Objective:** The main purpose of this study was to determine the clinical, radiological, pathological features, outcome and response to treatment in children with CGD. **Methods:** Thirteen patients with CGD, who were referred to the National Research Institute of Tuberculosis and Lung Disease (NRITLD) in Iran, were reviewed during a six-year period (1999-2005). **Results:** There were 10 (76%) male and 3 (24%) female cases. The median age of the patients was 9.5 years. Family history of CGD was reported by 7 patients. The median diagnostic age was 6.8 years, with a diagnostic delay of 4.6 years. The most common manifestations of CGD were pulmonary infections and skin involvement, followed by generalized lymphadenopathy. Diagnosis was based on reduced nitroblue tetrazolium test (NBT) between 0-10% in all patients and confirmed by the dihydrorhodamine (DHT) assay in 7 patients. The most common radiological findings were multiple lymphadenopathy in the mediastinal region and fibrotic changes in lung fields. Two patients died of pulmonary infections and 11 children are under observation and receiving prophylactic treatment including sulfamethoxazole-trimethoprim and itraconazole. **Conclusions:** Based on the results of this research, immunologic evaluations, especially evaluation for CGD, are highly recommended in children suffering from recurrent pulmonary infections, cutaneous or hepatic abscesses, or infections caused by uncommon pathogens such as *Aspergillus* and granulomatous lesions not attributed to any infectious agents. Early diagnosis and prophylactic treatment both prevent further development of the lesions and irreversible complications and decrease mortality and morbidity rates in children suffering from CGD.

Keywords: chronic granulomatous disease, children, infection

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INTRODUCTION

Chronic granulomatous disease (CGD) is a rare inherited disorder in which antimicrobial activity of phagocytes is impaired due to the lack of reactive oxygen species, or oxidative burst, produced by NADPH oxidase. The diagnosis of CGD is generally based on the clinical characteristics of the disease plus defective NADPH-oxidase activity as demonstrated by abnormal nitroblue tetrazolium (NBT), dihydrorhodamine 1,2,3, or superoxide release assays. Respiratory burst activity is a new method for measurement of neutrophil activation by minimal sample manipulation oxidative burst. [1-9]

The hallmark of this genetic disorder (X-linked or autosomal recessive, 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. According to the Winkelstein report, the annual incidence of CGD is estimated to be 1 in 200,000-250,000 live births. [4]

A study performed on 168 patients in the United States (Johnston 1999) showed that the most common clinical findings were marked lymphadenopathy, pneumonia and dermatitis. [5] Many patients are diagnosed in the first year of life, but there are some reports of late onset of CGD. [6,7] According to a study in Iran, the median age at onset of symptoms was four months, and the median diagnostic age was 5.5 years. [8]

The aim of this research was to describe the clinical, radiological, laboratory and evaluated characteristics of 13 patients with CGD admitted to the Pediatric Ward of the National Research Institute of Tuberculosis and Lung Disease (NRITLD).

MATERIALS AND METHODS

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

Medical history including personal and familial history, physical examination data, growth and development chart,

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and site of infection at the time of admission were obtained in all patients. Results of laboratory tests and radiological and CT-scan findings from the site of involvement were assessed and classified.

Induration of tuberculin skin test (Mantoux test by intradermal injection; 0.1 ml of 5 tuberculin units) was noted in all 13 patients.

NBT (Nitroblue tetrazolium test) was also divided into three categories as follows:

1- 0-10% (regarded as positive)

2- 10-90%

3- 90-100%

This is a descriptive case-series study. Data analysis was accomplished using the SPSS statistical software package (version 13.0).

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±4.8 (median=10, 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. In another 3 patients, no symptom was detected until 2 years of age. In a single 12-year-old male case, drug-resistant pneumonia was reported as the first manifestation of disease.

The mean age at diagnosis of disease was 6.8±4.6 (median=7.0, range=14.7) years, and mean duration between the onset of first symptom and diagnosis of disease was 4.6±3.9 (median=3.5, range=12.4) years.

In 12 patients, the growth curve was below 5%, while in one case the curve was at 10%.

In 3 patients with osteomyelitis, 2 had rib involvement and 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

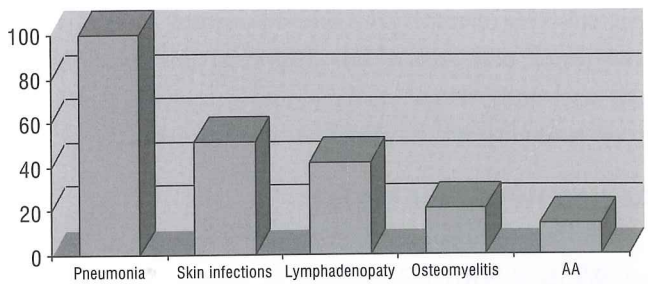

Figure 1 shows the clinical manifestations. AA: Abdominal abscess.

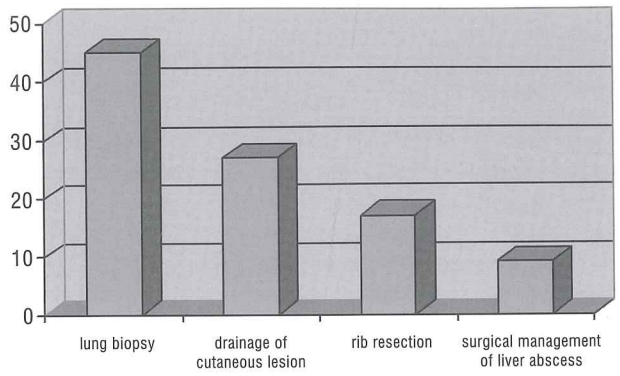

Figure 2 demonstrates the surgical procedures performed on the patients. Based on pathology reports, a granulomatous lesion was described in all of the cases.

obtained from the rib of 1 patient. The radiological (chest X-ray) and CT scan manifestations are shown in Table 1.

In regard to laboratory findings, NBT test was performed in all patients and was less than 5% in 3 (1 male, 2 female) while in the rest of the cases it was 0%. In 7 patients, detection was carried out by the dihydrorhodamine (DHR)-1,2,3 assay, which measures on a per-cell basis the NADPH oxidase-dependent oxidation of DHR by phagocytes. Normochromic, normocytic anemia and leukocytosis were reported in all the patients.

In this study, 2 patients (1 14-year-old boy and 1 11-year-old girl) died as a result of progressive, non-resolving pneumonia. In the remaining 11 cases, prophylactic regimen (itraconazole and cotrimoxazole) was administered and patients are under follow-up. Table 2 provides a summary of the CGD cases seen at our institution from 1999-2004.

DISCUSSION

Chronic granulomatous disease is a disease that is transmitted genetically by X-linked and autosomal recessive (AR) form. [1-9] The X-linked form of the disease accounts for about 70% of the patients.[6] In this research, the male population accounted for two-thirds (76%) of the total population, and would include the genetic transmission (X-linked). Since all female patients are not transmitted by AR pattern, evaluation of the patient's genotype is not possible without genetic investigations. [10]

Table 1. The radiological (chest X-ray) and CT scan manifestations

Multiple pulmonary lymphadenopathies	5	cases
Pulmonary fibrotic changes	2	cases
Pulmonary infiltration	2	cases
Rib involvement	2	cases

Table 2. Summary of CGD cases, 1999-2004

No.	Sex	Age (year)	Onset of first symptom (year)	Age of diagnosis (year)	Organ involvement	Fungal infection	NBT	DHR	Outcome
1	Male	5	3 months	3 month	Lung, Skin, Bone, Liver	Yes	0	3.2	Under observation
2	Female	11	3 months	2	Lung	Yes	0	-	Expired
3	Male	14	3.5	9	Lung, Liver	Yes	0	5.3	Expired
4	Male	15	7 months	13	Lung, Skin	No	0	-	Under observation
5	Male	5	1	4.5	Lung	No	0	-	Under observation
6	Male	14	3	9	Lung, Skin, Bone	No	0	-	Under observation
7	Male	3	3	3	Lung	No	0	-	Under observation
8	Male	15	12	15	Lung	No	0	7.9	Under observation
9	Male	10	2.5	7	Lung, Skin	No	<5%	4.4	Under observation
10	Male	15	1	13	Lung, Skin, Liver, Bone	No	0	2.6	Under observation
11	Male	8	1 month	7	Lung, Skin, Bone	Yes	0	-	Under observation
12	Female	4	1 month	3	Lung, Skin	No	<5%	2.9	Under observation
13	Female	3	3 months	3.5	Lung, Skin	Yes	<5%	1.8	Under observation

NBT: Nitroblue tetrazolium test (Normal value: 90%-100%). DHR: Dihydorhodamine (Normal value: 50-80).

Different studies have shown that 70% of patients are affected with at least one infection before two years of age. Similarly, as demonstrated in our research, 77% of the patients displayed serious clinical manifestations before two years of age. [11,12,13]

In neonates with CGD, despite the transmission of maternal antibodies, the phagocytic system of the patient is disturbed and newborns face various acute infections in the first few months of life.[14,15,16] Regarding the result of this research, 38% of the patients acquired their first serious infection before three months of life.

The diagnosis of CGD is delayed due to multiple features of the infection.[17]

The mean diagnosis age in this research was 6.8 years and delay in diagnosis was 4.6 years. In a study conducted by Finn et al. in England, delays in diagnosis in 1960 and 1980 were reported as 4.6 years and 1.5 years.[18] Respectively, in another investigation performed on 41 patients in Iran, delay in diagnosis was 3.8 years.[19] When our study is compared with the above-mentioned studies, it is easily deduced that there is a large difference between the diagnosis delay in our country and that of developed countries, a fact that requires more attention.[20]

Winkelstein and co-workers performed a study on 368 patients in the United States.[21] According to their results, pneumonia was the most common clinical manifestation; cutaneous infections and lymphadenopathy were observed in more than 50% of the patients. Comparably, 100% of our studied patients reported recurrent episodes of pneumonia that were resistant to treatment. Cutaneous infections and lymphadenopathy were recounted as 52% and 48%, respectively. According to these findings, CGD should be considered in each of the above-mentioned manifestations.

In our study, *Aspergillus* was detected in the pulmonary secretions of 38% of the patients; this rate being reported as 10-41% in other studies.[22] Furthermore, among CGD patients with history of pneumonia, more than 40% suffered from *Aspergillus* pneumonia at least once.[22] Additionally, in three patients with *Aspergillus* pneumonia, bone involvement was demonstrated, showing the high inclination of this fungus to involve the bone.[23] In two cases, rib resection was performed. Fungal osteomyelitis should be considered in patients suffering from *Aspergillus* pneumonia.

In spite of the relatively high mortality rate in CGD, most of our patients are alive (84%); two expired due to drug-resistant pneumonia. Since our study was conducted among children, the results cannot be generalized.

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 CGD, in children that suffer from recurrent episodes of respiratory and cutaneous infections with uncommon pathogens. Early diagnosis, antibiotic prophylaxis and anti- fungal medications (itraconazole) will decrease mortality and morbidity in these patients.

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