

# RESPIRATORY MANIFESTATIONS OF CHRONIC GRANULOMATOUS DISEASE; A CLINICAL SURVEY OF PATIENTS FROM IRANIAN PRIMARY IMMUNODEFICIENCY REGISTRY

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## ABSTRACT

Chronic granulomatous disease represents a group of inherited disorders of phagocytic system wherein recurrent infections are seen at different sites especially in the respiratory system. To determine the clinical spectrum of respiratory manifestations in chronic granulomatous disease patients, in this retrospective study, we used data from Iranian Primary Immunodeficiency registry. The diagnosis was based upon WHO criteria for chronic granulomatous disease. We reviewed the records of 38 patients (26 males, 12 females), related to 33 families, 73% of whom were consanguineous. The median age at the time of the study was 12yrs (3mo-22yrs). The median onset age of symptoms was 4 months (1mo-12yrs), and that of diagnostic age was 5yrs (1mo-20yrs), with a diagnostic delay of 4.15 yrs, on an average. Sixty three percent of our patients had respiratory involvement in the course of their illness, including pneumonia (18pts, 75%), tuberculosis (11pts, 46%), aspergillosis (3pts, 12.5%), pulmonary abscess (3pts, 12.5%), and bronchiectasis (1pt,4%). Only 4 of our patients presented with respiratory problems as their first manifestation. Lymph nodes were the first common site and the lungs were the second sites of involvement in chronic granulomatous disease patients; however, it is noteworthy that only in a few of our patients, it was the first manifestation of the disease. Thus special attention should be paid to the pulmonary complications while managing this disease.

**Keywords:** Chronic granulomatous disease, Respiratory manifestations

# Chronic Granulomatous Disease

## INTRODUCTION

Chronic granulomatous disease (CGD) is characterized by recurrent purulent infections of the skin, reticuloendothelial organs and lungs associated with an inability of patients' phagocytes to kill bacteria that do not produce hydrogen peroxide (2).

Most CGD patients have at least one unusual or severe infection during the first year of life and more than 80% are identified by unusual susceptibility to serious infections before their second birthday (6). Pulmonary disorders occur in nearly all children affected by CGD and includes recurrent pneumonia, hilar lymphadenopathy, empyema and pulmonary abscess (5). As antibiotic treatment does not result in rapid clearing, pulmonary infiltrates persist for weeks or months. (6) Fungal pneumonia is not uncommon. Aspergillus infections appear aggressively as extension from the lungs to the chest wall has been seen in several instances (7). As a result of improvement in controlling bacterial infections due to antibiotic prophylaxis and treatment; invasive fungal infections, especially the ones of aspergillus species, are now major causes of life-threatening infections in CGD (7).

The purpose of the present study has been to determine the clinical spectrum of respiratory manifestations in CGD patients referred to our center during a period of 20 years and to provide a more detailed survey about pulmonary infectious complications of this respiratory disorder.

## PATIENTS AND METHODS

The data was gathered from the records of the Iranian Primary Immunodeficiency (IPID) registry and database. Medical records of all patients with CGD diagnosed at Children's Medical center Hospital and Masih Daneshvari Hospital from 1980 to 2000 were reviewed. The diagnosis of CGD was made according to the standard WHO criteria, including a negative quantitative nitro blue tetrazolium test and total failure of chemiluminescence after phagocytosis.

Forty five patients met the above mentioned criteria and of these, 38 had been followed up and had adequate medical records to enter the study.

## RESULTS

### DEMOGRAPHIC DATA

Based on the above-mentioned criteria for diagnosis of CGD done at Children's Medical Center Hospital and Masih Daneshvari Hospital, 38 patients were diagnosed as having CGD. There were 26 males and 12 females, related to 33 different families, 73% of whom were consanguineous.

### ONSET AND DIAGNOSIS

The median age of patients at the time of the study was 12 years (3 months to 22 years). The median age at the time of disease onset was 4 months (1month to 12 years)(fig.1), and that of diagnostic age was 5 years (1month to 20years)(fig. 2). On an average, the diagnostic delay in our patients' group was 4.15 years. By the year 2000, 4 patients were dead and 13 patients could not be located, with an overall mortality rate of 10.52 %.

### CLINICAL FEATURES

Lymphadenopathy, respiratory involvement and skin infections were the most common complications of CGD and after them, gastrointestinal and skeletal problems were seen in significant cases (fig. 3).

Twenty-four out of 38 patients (63%) developed pulmonary involvement at sometime during the course of their illness, but only 4(10.5%) of them presented with respiratory problems as their first manifestation of the disease, for which an average diagnostic delay was 3.75 years (Comparing with 4.15 years overall diagnostic delay). Eighteen out of the 24 patients who developed respiratory complications were male.

Out of the 4 dead patients, 3 had pulmonary problems (2 pneumonia, 2 TB, no patients with Aspergillosis or bronchiectasis).

Out of the 24 patients with CGD who had respiratory manifestations, 18 patients (75%) had pneumonia (M/F ratio: 14/4), being the most common pulmonary complication. Eleven patients (46%) had tuberculosis (M/F: 7/4) that was established by positive sputum smear test. Aspergillosis was seen in 3 patients (12.5%) (M/F: 2/1) that were diagnosed by lung biopsy and positive culture, and other 3 patients (12.5%) were

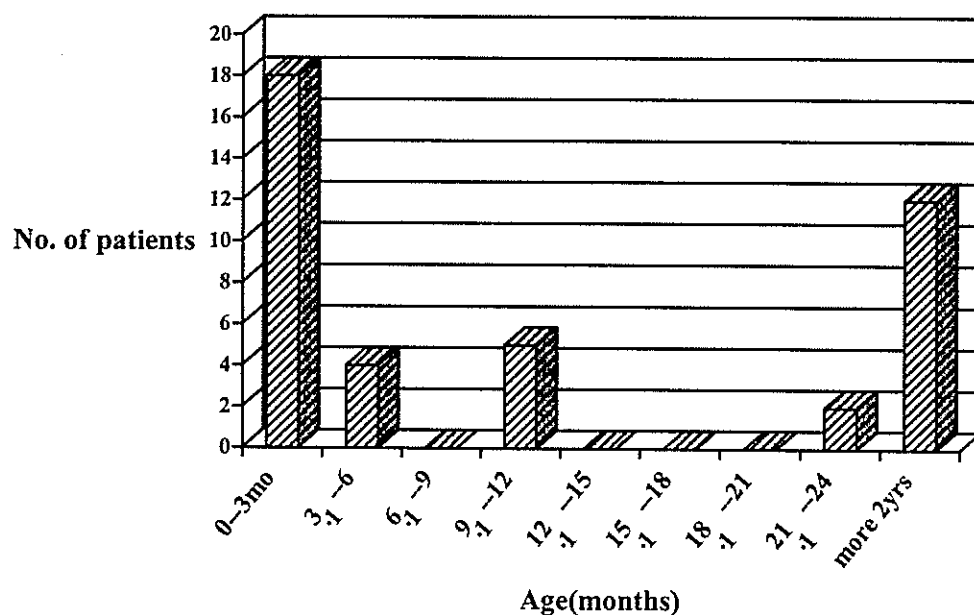


Fig. 1. Age of onset of symptoms in 38 patients with Chronic Granulomatosis Disease

complicated with pulmonary abscess. (M/F: 2/1). Bronchiectasis was detected in only one man with CGD (4%)(fig. 4), the diagnosis of which was based on the clinical symptoms, CXR, and finally HRCT. We did not screen our patients for bronchiectasis and did not perform HRCT for all of them, so there might have been more cases with bronchiectasis.

Two patients had tuberculosis and aspergillosis together and combined tuberculosis and pulmonary abscess was detected in 3 patients (M/F: 2/1).

## DISCUSSION

CGD is a condition known to be associated with repeated and life threatening bacterial and fungal infections at multiple sites such as lymph nodes, gastrointestinal tract and specially lungs. CGD is a rare syndrome. In 1997 an Australian group reported its prevalence about 0.8 in 1000000 births (17) and in 1999 Hasui reported CGD's prevalence as 1 in 287709 live birth in Japan(18). While respiratory complications have been one of the most commonly reported complications of CGD, most reports have been either single case or small series. In this study we have evaluated 38 patients affected by CGD who were referred to our center during a period of 20 years because of the presence of respiratory complications.

In our study, the male to female ratio (M/F) was 2.16 and the lungs were the second common sites of involvement after lymph nodes. Twenty-four out of 38 patients (63%) had respiratory manifestations. In some other studies respiratory manifestations have been stated to be the most common one (11). In Gallin JI 's study in 1983, 14 patients were evaluated and 8 patients (57%) had respiratory involvement and in the study done by Johnston RB (6) 27 out of 27 (100%) patients had respiratory manifestations. In a study done by Barbouche et al, 10 cases out of 14 CGD patients had pulmonary infection (71.4%)(16). Thus as shown in several articles, it is obvious that respiratory manifestations are common in CGD patients.

Patients affected by the classic form of CGD will begin to develop infections early in life sometimes even within the first week, but usually during the first year (5). In this group the median onset age of symptoms was 4 months (range 1 month - 20 years), and 26 out of 38 patients (68.4%) were one year old or less when the first symptom manifested. In a survey, which was done by Johnston RB and Newman SL in 1977, 109 out of 140 patients developed their first symptom by the first year of their lives and 125 cases by the age two. In a research done in Tunisia by Barbouche et al the

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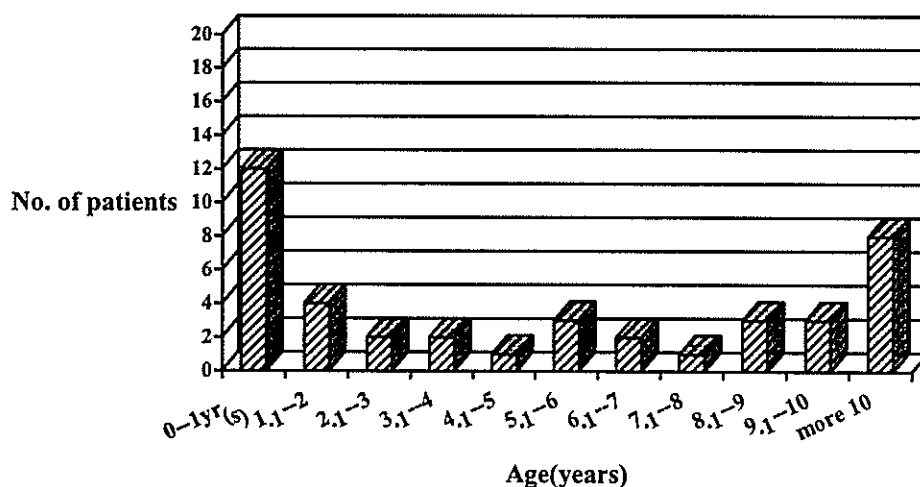


Fig. 2. Diagnostic Age of Disease in 38 Patients With Chronic Granulomatosis Disease

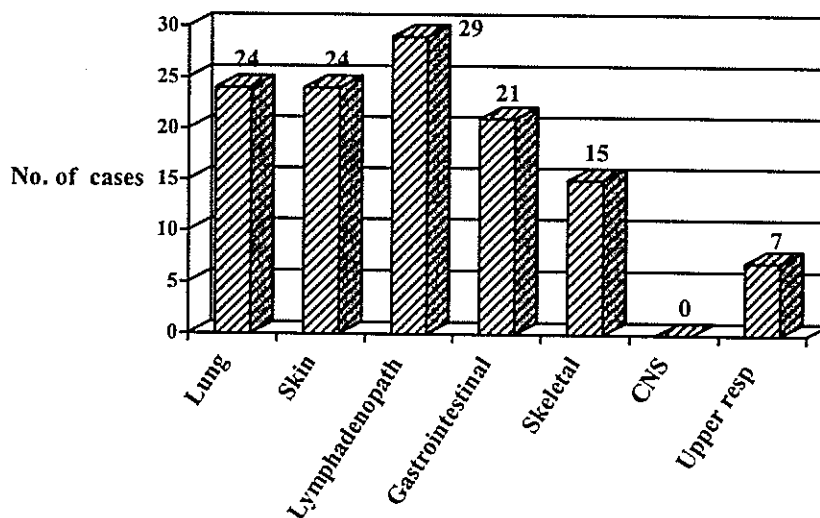


Fig. 3. Different organ involvement in 38 patients with Chronic Granulomatosis Disease

median onset age of clinical signs was 6.8 months (7days to 24 months) (16). Although the newborn with CGD receives antibodies from the mother, the phagocytes are its own. Thus he is in jeopardy from infections from the first moments of birth (2).

The respiratory involvement as the first manifestations occurred in only 4 cases (10.5%) so it is interesting that although respiratory involvement is common all throughout the life of the patients but respiratory manifestations as the first symptoms are unusual.

The average diagnostic delay of our patients was 4.5 years. The diagnostic delay is the time when the first symptom occurs until the diagnosis is achieved.

In a study done by Finn et al in London the mean diagnostic delay was reported to be 1.5 years in 1980s in comparison with 4.6 years in 1960s (9). This long diagnostic delay period maybe due to the insignificant and unspecific symptoms of the disease which the practitioners do not notice, even if the patient becomes complicated or shows symptoms for several times or has a sibling who has been diagnosed before. Moreover, our CGD patients had been referred from other hospitals in Iran to Children Medical Center and it could be the reason for the long diagnostic delay in our patients.

According to the study the respiratory involvement in our patients included pneumonia,

tuberculosis, aspergillosis, pulmonary abscess and bronchiectasis. Pneumonia was the most common complication (18 patients, 75%) and bronchiectasis was the rare one (1 patient, 4%).

According to Johnston RB & Newman SL survey on 168 patients with CGD, pneumonitis was the most common respiratory involvement (2). Based on a review by Tauber et al in 1981, 195 out of 245 cases of CGD patients developed pneumonia which was the most common clinical presentation (5). Some other studies have also shown that pneumonia has been the most common involvement (1, 4, 6), this is probably because of the easy exposure of the organ to the external pathogens such as bacteria, fungus and virus.

The dominant problem in all the patients whose lungs were the first site of involvement was pneumonia. Moreover, two out of the four of dead CGD patients had experienced pneumonia several times in their lives.

In our group of patients, pulmonary tuberculosis was the second common respiratory involvement (11 patients, 46%). In other studies this infection did not seem to play a significant role among the CGD patient infections (2, 4, 6). In their 1977 review, Johnston & Newman reported 4 out of 125 cases with CGD to have mycobacterial infection (2), and according to that of R. Mouy study in 1988 over 48 patients with CGD, 8 cases developed mycobacterial infection. In some studies respiratory tuberculosis has been mentioned as case reports. For example Ohga et al reported a 10- months- old Japanese male infant with *Mycobacterium avium* lesions in the lung as a clinical presentation for the onset of CGD (20). We suppose that the high rate of TB infections is due to high prevalence of TB in our country and because our patients are more exposed to mycobacterium tuberculosis. This common occurrence of Mycobacterial pneumonia in our CGD cases suggests a special attention and accurate prophylaxis of TB infections in Iranian CGD patients. Furthermore, BCGosis as a generalized lymphadenopathy following BCG vaccination is almost a common complication in these patients (15.7%). So BCG vaccination should be avoided in patients with diagnosed or suspicious CGD.

The prolonged survival of the children affected because of antibiotic therapy will increase the risk of parasitic and fungal infection (13). In cases with CGD several episodes of aspergillus pneumonia can occur and effective immunity to the organism does not develop after infection (7). Because of the need for biopsy for diagnosis and appropriate treatment of fungal infections, it is difficult to diagnose these infections in cases with CGD. In our study aspergillus infection was observed in 3 patients (12.5%), 2 are still alive and the third one's status is unknown. In 1977, Johnston & Newman reported that 13 out of 125 patients with CGD had involvement with aspergillus (7). In their survey of 245 cases with CGD, Cohen et al found that 50 patients had a history of fungal infections, 78.4% of which were caused by aspergillus. (12) Also 19 out of 48 patients (40%) studied by R. Mouy et al were infected by aspergillus (4). In D.S. Chudwin et al experience 4 of the 13 CGD patients followed up for 10 years, developed aspergillus pneumonia. In a survey of Eppinger et al in United States, 67% of CGD patients and hyper IgE syndrome cases were sensitized to aspergillus fumigatus-specific antibodies. Five of these had radiologic abnormalities consistent with a diagnosis of Allergic Bronchopulmonary Aspergillosis (19). The mean age at onset of the aspergillus infection in that study, was 7.5 years (range 6 to 10 years) (7).

CGD is associated with recurrent pyogenic abscess formation in regional lymph nodes, pulmonary parenchyma, and liver requiring surgical drainage (15). Three of our patients manifested pulmonary abscess during the period of their disease. TB infected all of these patients, and one of them had a history of aspergillus infection. One died at the age of 20 years. The mean onset age of them was 4 years and 2 months and that of diagnostic age was 7 years and 11 months. In two of these patients, the first clinical manifestation was lymphadenopathy and that of the third was pneumonia. None of these 3 patients had a history of satisfactory antibiotic prophylaxis and treatment over the period of their disease. On the other hand the patients who had received antibiotic prophylaxis did not complicate with pulmonary abscess.

Finally one of our cases had bronchiectasis as a

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respiratory manifestation. His first manifestation was pneumonia and the onset age was 12 years. Bronchiectasis was detected on chest X-ray.

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 so 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 (5).

A multifaceted therapeutic approach has been responsible for the greatly improved prognosis in CGD. The key elements of the current therapy include: 1. avoidance of certain sources of pathogens, 2. use of prophylactic trimethoprim-sulfamethoxazole or dicloxacillin, 3. early use of parenteral antibiotics including antifungal drugs, 4. surgical drainage or resection of localized abscesses and granulomas, 5. granulocyte transfusions for poorly responding infections and 6. the use of prophylactic recombinant human IFN- $\gamma$  (r IFN- $\gamma$ ) (3).

## CONCLUSION

Although respiratory involvement is common among the patients with CGD this occurred only in a few of our cases as the first manifestation. Pneumonia is the most common pulmonary disorder especially in the first year of life but pulmonary abscess and unusual infections such as mycobacterium tuberculosis and aspergillus may guide us to a serious of substantial immunodeficiency disorders like CGD. Special concern should be made to the pulmonary complications on managing this disease.

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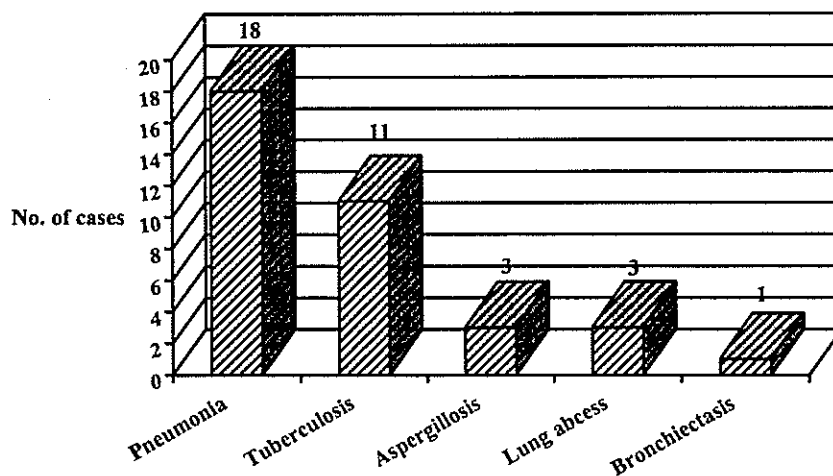


Fig. 4. Different lung manifestations in 38 patients with Chronic Granulomatous Disease

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