

Clinical and laboratory aspects of chronic granulomatous disease in description of eighteen patients

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To describe the epidemiological, clinical, laboratory, and evolution characteristics of 18 patients with chronic granulomatous disease (CGD). In this retrospective study, clinical, laboratory, and epidemiological data were obtained from the medical records of all patients with CGD seen at the Allergy and Immunology Unit of the Pediatrics Department (School of Medicine, University of Sao Paulo) from January 1979 to December 2001. Medical history and physical examination data, personal and family history, presence of consanguinity, weight and height data, presence of hepatosplenomegaly, adenomegaly, or other relevant alterations at the time of admission were obtained for all patients. We reviewed 18 patients (male:female, 8:1) with a median duration of symptoms of 1.25 months and with a median time since diagnosis of 13 months. A family history of death as a result of infection was reported by three patients and five other patients had a common relative with CGD who was included in the series. The clinical manifestations observed were: failure to thrive, adenomegaly, hepatosplenomegaly, pneumonia, and abscesses. Relevant laboratory data were hypergammaglobulinemia and nitroblue tetrazolium reduction test of 0% in 14 patients. Seven patients received IFN- γ and 11 sulfamethoxazole-trimethoprim. Six patients died of suppurative pulmonary infections. Age at the onset of symptoms was early, although diagnosis was late in some patients. Pulmonary involvement was the most prevalent clinical manifestation in the different phases of the disease and the major cause of death. Hypergammaglobulinemia, anemia, and leukocytosis were relevant laboratory data.

**Eugénia Grilo Carnide,
Cristina Abe Jacob,
Ana Moschione Castro and
Antonio Carlos Pastorino**

Pediatrics Department, Children's Institute, Sao Paulo, Brazil

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Dr Eugénia Grilo Carnide, Pediatrics Department,
Children's Institute, Sao Paulo, Brazil
Tel.: 55 11 3832 5213
Fax: 55 11 3069 8585
E-mail: gcarnide@uol.com.br; clinalerg@ig.com.br

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Chronic granulomatous disease (CGD) is a rare immunodeficiency caused by a defect of the enzyme nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) characterized by a reduced ability of neutrophils to destroy phagocytosed microorganisms. The prevalence of CGD varies among the populations investigated, with studies showing variations from one of 1,000,000 to one of 160,000 individuals (1).

The pattern of CGD inheritance can be X-linked (about 70% of cases) or autosomal

recessive (2). This immunodeficiency is characterized by repeated suppurative infections mainly located in the lungs, skin, and lymph nodes, but also affecting other organs (2, 3). The major agents involved in the infections are catalase-positive bacteria, mycobacteria, fungi, and other opportunistic germs (4).

The test most commonly employed for the CGD diagnosis is nitroblue tetrazolium reduction test (NBT), stimulated with substances such as phorbol myristate acetate (PMA) or *Escherichia*

coli lipopolysaccharide (LPS), which promote an oxidative response in 90–100% of normal neutrophils (4).

The authors report CGD patients admitted to the Allergy and Immunology Unit of the Department of Pediatrics (Faculty of Medicine, USP, São Paulo, Brazil) from January 1979 to December 2001.

Methods

Retrospective study based on the review of the patient's medical records in order to obtain clinical and epidemiological data including personal and family history and presence of consanguinity, as well as physical examination data with evaluation of weight–height according to the percentile curves of the National Center for Health Statistics (5).

The NBT test was used for the CGD diagnosis, with PMA or LPS stimulation, and the dihydro-rhodamine (DHR) test was applied to three patients.

The epidemiological, clinical, and laboratory data during admission and follow-up were obtained by review of patients charts.

Results

The study included 18 children (16 males/two females), age ranging from 15 days to nine months (median: 1.12 months) at the onset of symptoms. Age at CGD diagnosis ranged from 1 month to 16 yr (median: 1 yr and 1 month). The information about family consanguinity was possible in 12 patients and only one patient reported that her parents were first cousins. With respect to family history, three patients reported a history of siblings who had died of infection, without a diagnosis of immunodeficiency. One of the patients was the maternal uncle of five other patients, two of whom were twins. The pedigree of this family is presented in Fig. 1.

According to the clinical history, the most common initial manifestation was pneumonia, present in six of 18 children, followed by skin abscesses in five and adenitis in four. Acute otitis media was the initial complaint in three children. Patient distribution by weight and height percentiles is presented in Fig. 2. Other relevant data obtained by physical examination were adenomegaly in nine of 18, with three of these patients also presenting hepatosplenomegaly. Another patient had only hepatomegaly.

The types of infection detected in the patients are listed in Fig. 3. Lung involvement was the most frequent clinical picture, with three patients

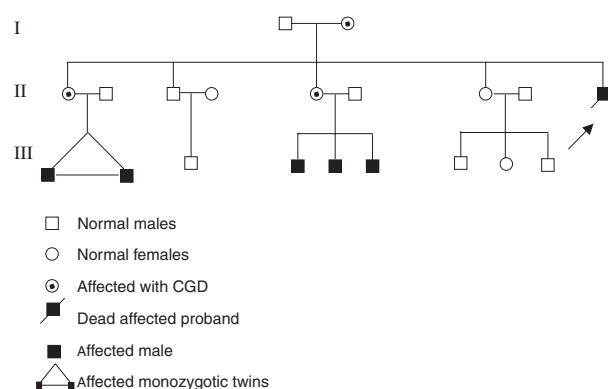


Fig. 1. Pedigree of a family with six patients.

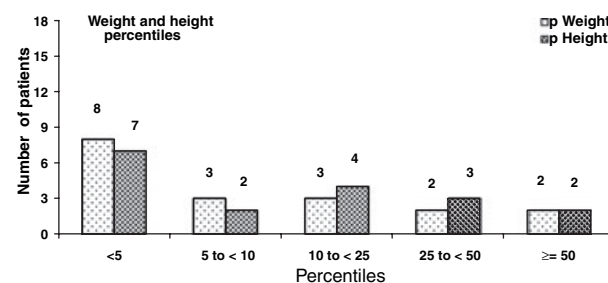


Fig. 2. Distribution of 18 patients with CGD according to weight and height percentiles (according to the National Center for Health Statistics).

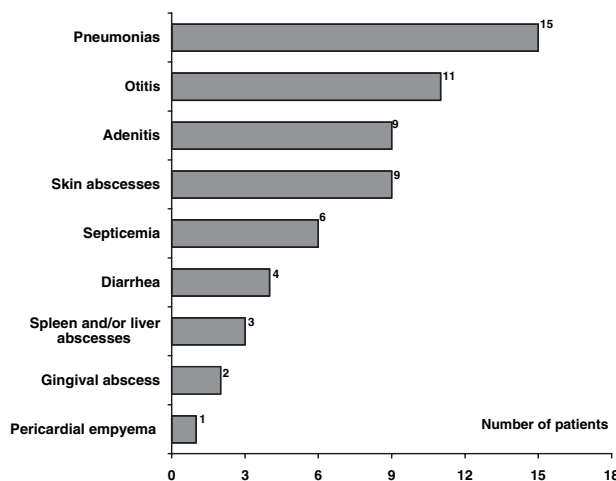


Fig. 3. Types of infection in the 18 patients with CGD during clinical follow-up.

presenting repeated pneumonia. Twelve patients had pneumonias that required hospitalization for intravenous antibiotic therapy and were considered to have severe pneumonias. Four of these patients presented pneumonias accompanied by pleural effusion. One patient had tuberculosis, diagnosed before he started ambulatory follow-up, as well as pleural effusion and bronchiectasia.

This diagnosis was based on suggestive radiologic changes associated with increased reactivity of the Mantoux test from 0 to 12 mm. Pulmonary abscesses were detected in two patients (Table 1).

One patient presented disseminated periorificial pustular skin lesions and liver and lung abscesses, requiring prolonged hospitalization for symptoms resolution. Fig. 4 shows the abdominal tomography of this patient, with several liver abscesses.

Of the 18 patients described, seven received IFN- γ irregularly, with one of them receiving it only during hospitalization for the liver abscesses treatment. Eleven patients received prophylactic sulfamethoxazole-trimethoprim (SMT). Six patients are currently being followed-up and six died. The causes of death were lung infections in all patients, and one patient also had endocarditis and purulent pericardial effusion because of *Staphylococcus aureus*.

The laboratory data obtained for the 18 patients are listed in Table 2.

The DHR oxidation test was performed on three patients and all of them presented an index of 1 for a reference value above 80.

Table 1. Pulmonary alterations in 15 patients with chronic granulomatous disease

Pulmonary alterations*	N	%
Severe pneumonias	12	80.0
Pleural effusion	4	26.6
Repeated pneumonias	3	20.0
Bronchiectasias	2	13.3
Pulmonary abscesses	2	13.3

*Some patients presented more than one alteration.

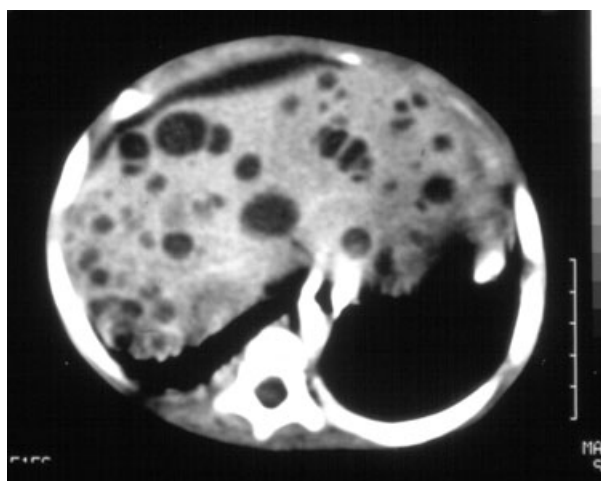


Fig. 4. Abdominal tomography of CGD patient showing hepatic abscess.

At least one infectious agent was isolated from nine of the 18 patients and the agents most frequently detected are listed in Table 3.

Discussion

Although this is a significant number of patients, it is still much lower than expected considering the number of births per year just in the São Paulo State. These data indicate that the disease is probably under diagnosed.

As expected, males predominated in this series, since X-linked inheritance corresponds to about 70% of CGD cases. Age at the onset of symptoms is early, usually during the first year of life. Finn et al. (6) described a series of 28 cases, in which 50% of the patients had their first infection before 1 yr of age and 79% before 2 yr of age. However, CGD can manifest later, mainly in patients with milder signs and symptoms who usually belong to the group of patients with autosomal recessive inheritance (7). In the patients reported here, age at first infection was <1 yr in all cases. Despite the early onset of symptoms, some patients received a later diagnosis, after the age of five in four cases. The later diagnosis of these patients may indicate faults of the criteria currently used as an alert to immunodeficiency, especially in cases of milder clinical manifestations.

The initial clinical manifestations of the disease vary among series, according to the reference center qualification. In the present study, pneumonias were the most common initial manifestation, followed by skin abscesses. However, according to some literature data, the most common initial manifestation is lymphadenitis (3, 8). Other initial manifestations have also been reported, mainly skin abscesses and pneumonias (3, 9).

The nutritional involvement detected in the present patients is a fact to be emphasized. Although Brazil is considered to be a developing country with great economic difficulties and important social differences, this is a finding also reported in other series belonging to developed countries (3, 9). This fact, associated with repeated infections of early onset, can be of help in differentiating the disease from humoral immunodeficiencies, in which the nutritional status is usually little affected and the clinical manifestations frequently occur after 6–9 months of life. Nevertheless, nutritional recovery is likely to occur when the patients are properly followed up, with prophylactic treatment and reduction of infections, as observed by Cale et al. (9).

Lung involvement is very common in CGD patients, with prevalence about 80% of all

Table 2. Laboratory evaluation of 18 patients with chronic granulomatous disease

Patient/Test	Anemia (hemoglobin <12.5 g%)	Leukocytosis (leukocytes >8.5 × 10 ³ /mm ³)	NBT post-stimulation (%)	Hypergamma globulinemia
CSB	No	No	10	No
GTP	NM	NM	0	Yes
TRS	NM	NM	0	NM
TRBA	NM	NM	0	NM
FJL	Yes	No	0	Yes
VGJ	Yes	No	2	Yes
LFRG	Yes	Yes	9	Yes
ESB	Yes	Yes	0	Yes
ACSA	Yes	Yes	2	Yes
GVGB	Yes	Yes	0	Yes
BTP	Yes	Yes	0	Yes
RCS	Yes	Yes	0	Yes
ERG	Yes	Yes	0	Yes
YHGS	Yes	Yes	0	NM
ARGS	Yes	Yes	0	Yes
HYGS	Yes	No	0	Yes
HLS	Yes	Yes	0	Yes
RRGB	No	Yes	0	Yes

NM, not made.

Table 3. Infectious agents and sites of isolation in nine patients with chronic granulomatous disease during clinical follow-up

Agent	Site of isolation				No. of patients*
	Skin + Lymph nodes	Heart	Respiratory tract	Blood + Catheters	
<i>Staphylococcus aureus</i>	—	1	—	4	4
<i>Serratia marcescens</i>	2	—	—	1	2
<i>Burkholderia cepacia</i>	—	—	1	1	2
<i>Pseudomonas aeruginosa</i>	—	—	2	—	2
<i>Enterobacter</i>	2	—	—	—	2
<i>Candida</i> sp.	—	—	4	—	4
<i>Acremonium killiensis</i>	—	—	1	—	1
<i>Mycobacterium</i> sp.	1	—	1	—	2

*More than one infectious agent was isolated from all patients.

reported patients in different series and associated with significant morbidity and mortality (1, 3, 8, 10). Pneumonias may progress to atelectasias and abscesses and extensive reticulonodular infiltration may lead to respiratory failure and death.

In the present study, pneumonias were also the most common clinical finding. The type of involvement also varied, with a predominance of severe pneumonias over repeated pneumonias. These data support the importance of pulmonary involvement in patients with CGD, which may not necessarily be the initial manifestation, but which evolves with growing severity along time, being the most important cause of death (3).

The development of serious infections is common in CGD, with some patients progressing to

septicemia (3). In the present series, six patients presented septicemia, an event that occurred before the diagnosis of CGD in all cases. This is one more result that emphasizes the necessity for an early diagnosis for the institution of effective therapeutic measures such as antibiotic treatment.

In patients with CGD, the formation of granulomas in various organs has been described as a marker of the disease. The onset of granulomas in hollow viscera may lead to obstruction, mainly in the gastrointestinal and urinary tracts. In the present series there was no symptomatology compatible with granuloma formation in hollow viscera, an interesting result considering the high prevalence of this finding in patients with CGD. However, Liese et al. (3) reported that granulomas mainly occur in older patients with some residual activity of the oxidative mechanism, possibly explaining the non-detection of granulomas in this study.

Anemia (hemoglobin <12.5 g%) and leukocytosis (leukocytes >8.5 × 10³/mm³) were common findings in the present series, as also reported by others (9). In some patients, leukocyte numbers continued to be elevated even when no acute infection occurred, indicating the possible maintenance of a chronic stimulus. Nevertheless, leukocytosis and increased blood sedimentation rate represent an alert to the fact that a more rigorous investigation of infectious processes should be performed in CGD patients.

Hypergammaglobulinemia, a common occurrence in our patients, has been a relevant finding since the first description of CGD by Janeway et al. (11) in 1954 and may serve as an alert to diagnostic suspicion when associated with the clinical manifestations described earlier.

Mycobacteria are agents known to affect CGD patients (4) and were detected in three of the patients. In general, all immunocompromised patients are at higher risk to develop fungal infections. The importance of fungi as infectious agent in CGD was demonstrated by Cohen et al. (12) in 1981. In this casuistic, fungi were isolated from the bronchoalveolar lavage of three patients, with *Candida albicans*, being most commonly detected. *Acromonium kiliensis* was isolated from the lung biopsy of one patient; this is a rare agent whose presence, however, has been previously reported in the literature (13). *Aspergillus* was not isolated from any of the present patients, a surprising fact if we consider that this fungus is frequently associated with infections in CGD patients.

The treatment of CGD involves, in addition to general care such as the prevention of infections and vaccinations (except BCG), the use of SMT in combination or not with itraconazole for prophylaxis. The patients described here were treated with SMT and/or IFN- γ , but not with antifungal agents as no infection with *Aspergillus* sp. was detected. Follow-up time and the small number of children with a longer and more regular follow-up do not permit us to draw any conclusions about the benefits of these treatments.

The authors emphasize the importance of early diagnostic and therapeutic intervention in CGD patients and suggest that in patients with severe and/or recurrent infections, especially of pulmonary localization, the diagnosis of CGD be included among the possible hypotheses.

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