CHRONIC GRANULOMATOUS DISEASE: KING HUSSEIN MEDICAL CENTER EXPERIENCE

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ABSTRACT

Objective: To describe a single center experience of a rare disease, with special emphasis on clinical presentation, treatment options and prognosis.

Methods: We retrospectively reviewed the files of 12 patients discharged with the diagnosis of chronic granulomatous disease between July 1997 and June 2004 in the pediatric immunology clinic at King Hussein Medical Center.

Results: Twelve patients, seven males, and five females were identified. They aged between 13-84 months at the time of diagnosis. The mean age of follow-up was 33 months. Eight patients were alive and four had died. Family history of Chronic granulomatous disease was positive in 10 patients. The mean duration of delay in diagnosis was 27 months. Two patients had Aspergillus chest infection; one tuberculosis meningitis and two had multiple liver abscesses. A microorganism isolates included Aspergillus species, Salmonella, Staphylococcal aureus, and Pseudomonas aeruginosa. None of our patients had non-infectious complications. All patients were failing to thrive at the time of diagnosis. Most of them achieved acceptable growth after 24 months of treatment. All patients received Trimethoprium-sulphamethoxazole and Itraconazole. None of our patients underwent bone marrow transplant. The duration of hospital admission was significantly decreased after treatment from a median of 19 weeks before to two weeks after treatment.

Conclusion: Awareness of general pediatricians toward early diagnosis was suboptimal. Every effort should be made to improve the laboratory diagnosis by using more specific tests. Anti-microbial prophylaxis improved the prognosis of chronic granulomatous disease significantly. Interferon-γ and bone marrow transplant should be considered for the patients with poor response to daily antimicrobial prophylaxis.

Key words: Chronic, Granulomatous, Disease, Diagnosis, Complications, Treatment.

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Introduction

Chronic granulomatous disease (CGD) is uncommon congenital Immunodeficiency with the incidence of one in 250,000 individual (1,2). It is caused by a profound defect in an oxygen metabolic burst that normally accompanies phagocytosis in all myeloid cells (1,2). As a result of the failure to activate the respiratory burst in their phagocytes, the majority of CGD patients suffer recurrent infections, the most common of which are pneumonia, lymphadenitis, cutaneous and hepatic abscess, osteomyelitis, and septicemia (1,2). These severe infections usually become apparent during the first year of life and are caused predominantly by Staphylococcus aureus, Aspergillus species, enteric gram-negative bacteria, Serratia marcescense, and Pseudomonas cepacia (1,3). In addition, CGD patients have diffuse granulomas that can become sufficiently large to cause obstructive or painful symptoms in esophagus, stomach, biliary system ureters, or urinary bladder (4,5). CGD is inherited as X-linked recessive in 65% of cases and autosomal recessive in 35% (2,3). Conventional treatment consists of lifelong antiinfective prophylaxis with antibiotics such as cotrimoxazole and antifungics such as itraconazole and/or with interferon gamma (6,7,8). Despite these measurements the annual mortality is still between 2 (autosomal recessive CGD) to 5 (X-linked CGD) percent (8). An alternative to conventional
treatment, hematopoietic stem cell transplantation (HSCT), should be done early before patients develop any irreversible organ damage. We reviewed 12 files of patients discharged with the diagnosis of CGD.

Methods

All files reviewed were of patients discharged with the diagnosis of chronic granulomatous disease (CGD) between July 1997 and June 2004 at the pediatric immunology clinic at King Hussein Medical Center (KHMC). The files were reviewed for demographics, age at presentation, clinical course after diagnosis, growth achievement, antimicrobial prophylaxis, and laboratory parameters. We initially diagnosed all cases by means of the phorbol myristate acetate-stimulated nitroblue tetrazolium test (NBT), and only one of them was confirmed by flowcytometry burst test using Dihydrorhodamine (DHR) dye (Fig. 1). Mutation analysis was not available in Jordan.

Results

Twelve CGD patients (7 males and 5 females) aged between 13-84 months (median 31 months) were identified between 1997 and 2004. The median duration of follow-up was 33 months. They all are permanent residents of Jordan and have Arabic racial pattern. These patients belonged to 6 families, and the parents of all patients were consanguineous. Most of our patients were diagnosed as late as 27 months after initial presentation.

None of them was diagnosed before the onset of symptoms or in the neonatal period even in those who had positive family history of CGD. Tables I and II show clinical and laboratory features at initial presentation. Four patients died (33.3%) during the follow up because of recurrent infections and complications, including acute disseminated aspergillosis (in a 4-year-old boy); he showed typical chest CT scan findings of acute pulmonary Aspergillosis (Fig. 2), sepsis after the rupture of multiple bacterial liver abscesses (in a 9-year-old girl), sepsis after pneumonia (in a 9-month-old boy), and acute miliary tuberculosis (in a 5-year-old boy). One patient had subacute bacterial meningitis. Cultures for bacterial, mycobacterium and aspergillus infections were negative. He was not vaccinated by BCG. The diagnosis of tuberculous meningitis was made because of Cerebrospinal fluid (CSF) lymphocytosis, poor response to antibacterial therapy, dramatic response to 9 months of triple anti-tuberculosis regimen and proved contact with patient with active tuberculosis. He recovered with moderate communicating hydrocephalus (Fig. 3). Another female patient presented at 5 months of age with severe respiratory distress. Chest X-ray and CT scan showed mass-like lesion with rib involvement (Fig. 4). The mass was surgically removed, and proved to be aspergilloma containing Aspergillus fumigatus. She continued to be well on trimethoprium-sulphamethoxazole and Itraconazole prophylaxis. A newly diagnosed 9-year-old boy presented with multiple liver abscesses of variable sizes (Fig. 5). Surgical drainage was performed due to failure of response to medical treatment. None of our patients had non-infectious complications. All patients were failing to thrive at the time of diagnosis. Five patients (42%) achieved acceptable weight and height gain after 2 years. All patients received trimethoprium-sulphamethoxazole and Itraconazole prophylaxis for bacterial and Aspergillosis at the time of diagnosis. They all tolerated treatment well. The median duration of hospital admission for major infection was two weeks (ranges 2-5 weeks) with prophylactic treatment compared to 19 weeks (range between 12-29 weeks per patient per year) before treatment. None of our patients underwent bone marrow transplant and none of them received Interferon-gamma as prophylaxis or as treatment agent. Purified protein derivative (PPD) was negative in all patients at initial presentation. The microorganisms isolated were Aspergillus species.

Fig. 1. A. Flow Cytometry-based burst test display dihydrodramine (DHR) fluorescence in a patient with CGD. A: positive control (normal), B: Patient result shows abscence of fluorescence activity. Adapted with permission from Al-Wahadneh et al. JBMS 2001; 13(2): 101-105.
Salmonella species, Staphylococcal aureus and Pseudomonas species. All patients had high ESR and CRP during exacerbation, which are decreased significantly in most patients after treatment. All patients remained anemic despite tonic supplement.

Fig. 2. Chest CT scan of a male with CGD and Aspergillus infection

Fig. 3. Brain CT scan shows moderate dilatation of the ventricular system associated with persistent extravasation of the CSF. Appearances are those with moderate communicating hydrocephalus.

Fig. 4. Chest CT scan of a female with CGD and Aspergillus infection (Asperigelloma) spread contagiously to ribs.

Fig. 5. Abdominal CT scan showing Hepatic abscesses.

Discussion
To the best of our knowledge, this report was the first on Jordanian CGD patients comprising the clinical data of 12 patients in a single center during 8-year period. Male patients constituted 58% of our patients. The male to female ratio in our study (1.4:1) was lower than that in other studies, which may be due to higher autosomal inheritance related to increased consanguinity of families in Jordan. Two out of six families showed X-linked mode of inheritance, while the other four showed autosomal recessive pattern. These findings were in keeping with similar studies in Iran and Tunisia, 2.4:1 and 1.8:1 respectively (16,17). However, the relative preponderance of X-Linked cases compared with autosomal recessive CGD cannot be precisely defined in our series. We do not have mutation analysis in our laboratory, and although
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our patients. Pulmonary tuberculosis was documented in
one patient who died of acute miliary Tuberculosis
without previous BCG vaccination (16-19). The incidence
of pulmonary tuberculosis in patients with CGD is
variable; some reported as high as 32% of cases, while
others found that this infection did not play a significant
role among the CGD patients (4, 16-19). This might be due to
the difference in exposure to Mycobacterium tuberculosis
in different countries (4, 16-19). Aspergillus
neumonia had been identified in two patients (16%);
this is in keeping with other reports that found that the
incidence of Aspergillus pneumonia ranged between
7-10% (4, 16, 17). It might be attributed to the improvement
in controlling bacterial infections by antibiotic
prophylaxis, which makes the invasive fungal infections;
especially the ones of Aspergillus species are now the
most important causes of morbidity and mortality in
CGD in spite of Itraconazole prophylaxis (4, 16, 17).
Cellulitis and osteomyelitis were not documented in our
study, in contrast with other researchers who reported a
prevalence of 20% in their patients’ cohort (4, 16, 17). The
differences in the relative prevalence of infections
between different series may be related 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 reported (4, 16, 17). Despite data to show that good
preventive treatment improves survival and quality of life
in children, CGD is still associated with high morbidity
and mortality (4, 18). There were 4 deaths in our cohort; all
of them were found non-compliant to anti-microbial
treatment. Goldblatt reported that the incidence of severe
infections with prophylaxis was significantly low, at 0-11
per patient year follow up (19). We also achieved a
significant decrease in incidence of severe infection; it
decreased by 78%. We believe that the improvement in
Goldblatt and our series is due to proper coverage of both
bacterial and fungal microorganism (4, 16-20). The use of
interferon gamma was advised only when patients
develop severe deep infection despite oral treatment (21).
None of our patients had non-infectious complication
compared with other cohorts (3, 4). This is in keeping with
Finn et al who did not report any non-infectious
complications and Goldblatt and Cohen; who reported
less than 10% of their multi-center cohorts (3, 4). It could
reflect either a historical failure to distinguish infections
from non-infectious symptoms or a rare increase in the
non-infectious complication, in addition to the fact that
our patients were followed for a relatively short period of
time, where most inflammatory complications occurred
in the second decay of life (4, 16, 17). Prophylactic
antimicrobials are the main stay of treatment for patients
with CGD (3, 7, 21). However, serious breakthrough
infections are common (3, 7, 16, 17). These are encouraging
trials of bone marrow transplant early in life, before
the appearance of severe infections or irreversible
tissue damage, as a curative treatment with some
limitations (9, 16, 14, 15). We concluded that awareness of
general pediatricians toward early diagnosis was
suboptimal. Every effort should be made to improve the
laboratory diagnosis by using more specific tests. It
seems necessary for future studies to the genotype of our
CGD patient and improve the carrier screening of
X-linked cases in certain families for early diagnosis and
prevention of severe complications. Bacterial and fungal
prophylaxis improved the prognosis of CGD
significantly. Experience with Interferon-γ and bone
marrow transplant was substantial and should be
encouraged for patients with poor response regardless of
daily prophylaxis.
Table I. Demographic, clinical features, and treatment options of 12 patients

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+: Present  -: Absent  ?: not proved radiologically or microbiologically

Table II. Immunological laboratory tests.

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<td>1/1</td>
<td>1/1</td>
</tr>
</tbody>
</table>

H: high, N: normal, Abn: abnormal, NA: not available, -: negative. I: increased

References


