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Chronic granulomatous disease: Benghazi children's hospital experience

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***Abstract*---**Chronic Granulomatous Disease (CGD) is an uncommon inherited primary immunodeficiency, that can lead to life threatening infections due to defect in phagocytes to kill some microbes. The incidence is variable among different countries, and the clinical course range from mild to severe disease. This study was carried out to increase the awareness of the disease among medical media which is very deficit especially in the absence of diagnostic investigations in most centers in Libya. To the best of our knowledge, this survey can be considered as the largest Libyan study which demonstrated the clinical characteristics of 54 CGD patients. Male cases were 34 out of the surveyed patients. The parents were consanguineous in 30 CGD patients (55.6%). About 16 patients were from Benghazi city and 38 were from outside Benghazi. The most common manifestation in CGD patients was infection in the lymph nodes (87%), followed by skin infection (85%), infection in gastrointestinal tract (77%), lung infection

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(72%), BCG disease (44%), urinary tract infection and septicemia (33%), bone and joint infections (19%), inflammatory complications and brain infection (11%) and infection in the liver (9%). 33.3% of patients received antibiotic prophylaxis, and 40.7% received combined antibiotic plus antifungal prophylaxis, while 26% underwent hematopoietic stem cell transplantation (HSCT). The outcome was death in 66.6% of CGD patients who received antibiotic prophylaxis, and in 26.1% of those received antibiotic plus antifungal prophylaxis, and 38.5% of those who underwent HSCT died. The increase in mortality and severity for our CGD patients gives more insight about the importance of early diagnosis and starting treatment to prevent the fatal complications of the disease.

***Keywords*---**chronic granulomatous disease, primary immunodeficiency, CYBA gene, autosomal recessive, Libya, Benghazi.

Introduction

The first description of Chronic granulomatous disease (CGD) was in 1954, since the affected children had recurrent infections with elevated serum immunoglobulin levels (1). There is now much progress in understanding of clinical presentation and pathophysiology of CGD since its first description (2) CGD is a rare primary immunodeficiency disorder with recurrent bacterial and fungal infections, as a result of defect in the phagocytes to produce reactive oxygen species. The disease is caused by mutations in any one of the five components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme in phagocytes (3), and because of different mutations, the disease has a variable clinical presentation from a mild to a severe disease (4), and there is x-linked and autosomal recessive (AR) forms of CGD (5). In out bred populations, CGD affects approximately 1 in 130,000 to 250,000 live births (6,7), and in countries with high prevalence of consanguineous marriage the incidence of CGD may be higher, as well as the PIDs (primary immunodeficiency diseases) with AR inheritance (8,9). Libya is part of middle east and north Africa region, where consanguineous marriage is common with incidence ranging between 20 and 50% (10).

We conducted this study to increase the awareness of CGD among the pediatricians for early diagnosis, and so we aimed to study the variable clinical presentation that involve multiple organ systems, and the treatment options available for CGD patients in Libya. Patients affected with CGD had recurrent bacterial and fungal infections which may lead to granuloma formation, and are at an increased risk for inflammatory complications (11,12). Children with CGD usually present with recurrent infections in early childhood that include pneumonia, lymphadenitis, skin infections, diarrhea, sepsis, spleen and liver abscesses and osteomyelitis (13,14).

There are some investigations can help in disease diagnosis in patients with characteristic clinical manifestation of CGD. Nitroblue tetrazolium (NBT) test is used to measure the activity of NADPH oxidase (15). CGD can be diagnosed with

easy test which is more sensitive and more reliable than NBT by dihydrorhodamine (DHR) flowcytometry test (16,17). Genetic testing is important to detect the mutated gene (18). After confirming the diagnosis of CGD, treatment should be started immediately to prevent infections. Antibacterial prophylaxis with trimethoprim-sulfamethoxazole is advised to reduce the frequency of bacterial infections (19,20). Antifungal prophylaxis is given with itraconazole to reduce the frequency of fungal infections. However, CGD can be cured by hematopoietic stem cell transplantation (HSCT), and this effective therapy better to be done early in life before severe organ damage (21).

Methods

This study was descriptive case series of Libyan patients diagnosed with CGD who were admitted to Benghazi children's hospital, or those on regular follow up to immunology clinic as OPD cases in the same hospital. All patients with CGD managed in Benghazi children's hospital were included in this study, while we excluded two patients due to loss to follow up in one patient, and incomplete data in the file of the other patient. Data collection covered a period of ten years from February 2012 to December 2021. Informed consent for publication was taken from the patients' parents. Diagnosis of CGD was based on lab diagnostic tests by NBT or DHR, and characteristic signs and symptoms suggestive of CGD. Data were collected from the medical records for 54 patients, including Clinical history, physical examination findings, laboratory examination results including diagnostic tests of CGD by NBT and DHR, imaging findings, treatment and the patient outcomes. The statistical analyses were done using SPSS 25.0. Descriptive statistics were mainly shown.

Results

This study analyzed data of 54 children diagnosed as CGD cases, 63% of them were males and 37% were females. Parents consanguinity was positive in 55.6% and positive family history of similar illness was reported in 53.7% (table 1). Less than one third of the cases were from Benghazi (29.6%), Almarj city was the address of 18.5%, and 11.1% from Albaida, and other cases were from other eastern part of Libya as demonstrated in figure 1.

The most common infection in our CGD patients was in the lymph nodes, since 47 patients (87%) had at least one infection in the lymph nodes, followed by infections in the skin in 85% of patients, gastrointestinal tract (GIT) in 77% and infection in the lung reported in 72% of patients. Other less common infections were BCG diseases in 44%, urinary tract infection (UTI) and septicaemia in 33%, bone and joint infections in 19% of CGD patients. Inflammatory complications and infection in the brain were reported in 11%, while the least common reported infection was in the liver in 9% of CGD patients. (table 2)

Cotrimoxazole was used as prophylactic treatment by 18 cases (33%), Cotrimoxazol +Itraconazole prophylaxis by 22 cases (40.7%). HSCT was done for 14 cases (26%) (table 3). Outcome of the cases at time of data collection was death in 23 cases (42.6%) and still alive in 31 cases (57.4%) (table 3) Treatment type was studied against the outcome of cases (table 4), and the results suggested that

better outcome (survived) was observed in those who received a combination of Cotrimoxazole and itraconazole as prophylactic therapy as 73.9% were alive and 26.1% deceased. Then those who treated with HSCT as out of them 61.5% survived while 38.5% died. The worse outcome was seen in the cases who received cotrimoxazole, as 66.6% of them died compared to 33.3% survived (Chi-Square 6.920, P. value= 0.031).

Table 1: Socio-demographic characteristics of CGD patients

Variable		N	%
Gender	Male	34	63
	Female	20	37
Parents consanguinity	Yes	30	55.6
	No	24	44.4
Family history	Positive	29	53.7
	Negative	25	46.3
Residence	Benghazi	16	29.6
	Outside Benghazi	38	70.4

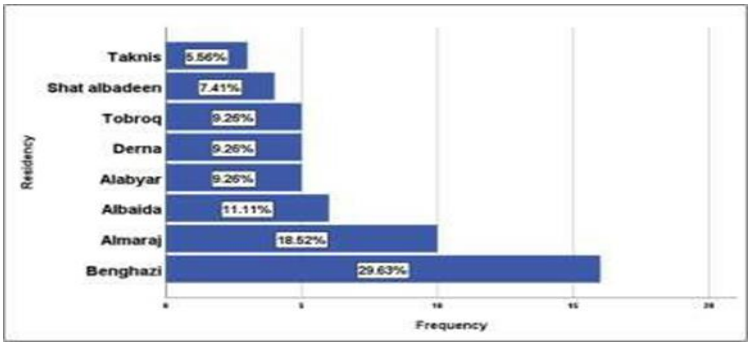

Figure (1): Distribution of the cases by city of residence.

Table (2) Site of disease in CGD patients

Disease site	Number of diseases in each site	Number of patients with ≥ one disease
Lymph node	91	47 (87%)
Skin	82	46 (85%)
Gastrointestinal tract	101	42 (77%)
Lung	85	39 (72%)
BCG disease	24	24 (44%)
Urinary tract	28	18 (33%)
Septicemia	18	18 (33%)
Bone/joint	10	10 (19%)
Inflammatory	13	6 (11%)
Brain	7	6 (11%)
Liver	6	5 (9%)

Table (3) Type of treatment received by the study cases and clinical course of the cases

Clinical characteristic		Frequency	%
Treatment	Cotrimoxazol prophylaxis	18	33.3
	Cotrimoxazol +Itraconazole prophylaxis	22	40.7
	Hematopoietic stem cell transplantation	14	26
Outcome	Alive	31	57.4
	Deceased	23	42.6

Table (4): Treatment type and outcome of the study cases

Treatment	Outcome		Total
	alive	Died	
Cotrimoxazole	6 (33.3%)	12 (66.6%)	18 (100%)
Cotrimoxazole + itraconazole	17 (73.9%)	6 (26.1%)	23 (100%)
Hematopoietic stem cell transplantation	8 (61.5%)	5 (38.5%)	13 (100%)
Total	31	23	54

Chi-Square: 6.920, P. value: .031

Discussion

Libya is a country with small population, and this is the largest study described CGD patients so far in Libya. The data of 54 patients collected from Benghazi children's hospital, which is the only center in the country has immunology unit taking care of patients with primary immunodeficiency diseases. The study represents mainly patients from eastern Libya, and 29.6 % of them are from Benghazi city. 37% of CGD patients were females, and this supports other reports that AR-CGD is more common than XL-CGD in Libya and other Arab countries, where consanguineous marriage is high (22,23,24,25). The consanguineous marriage was also high in our study, since parent's consanguinity was detected in 55.6% of patients.

Regarding the common sites of disease in our study, 47 (87%) patients had lymphadenitis which is the most prominent infection in our patients, followed by skin infections in 85%, and infection in the GIT in 77% of CGD patients. These infections were also common among CGD patients in other reports (6,26,27). Pneumonia was another common infection detected in our study, and it affected 72 % of our patients. Pneumonia was the most prominent infection among CGD patients in report from china (27) and the incidence of pneumonia was high in the United States and Japan (26,28), while it is less commonly reported from some European countries (29.30).

In Libya, all neonates are given BCG vaccine at birth, and 44 % of our patients had either regional or disseminated BCG infection which is more common than other reports from morocco and china (31,32) UTI, septicemia, infections in the bones or joints, inflammatory complications, CNS infections and liver abscess were also seen in our CGD patients, but with less common occurrence, and these infections were reported in CGD patients from other studies (6,26). 43.6 % of our CGD patients were deceased, and this increase in mortality in our study compared to other studies (33), perhaps due to less number of patients received antibiotic plus antifungal prophylaxis (40.7%), which also explains the increased number of infections in our patients. The worst outcome was in 18 patients, who had antibiotic prophylaxis only, since 12 patients of them deceased (66.6%). This group without antifungal prophylaxis are at increased risk of pulmonary aspergillosis and death (34). Only 26% of patients had HSCT which is curable therapy for CGD (21). Currently there is no center for HSCT in Libya, and it is expensive to be done outside the country, so it is not available as therapeutic option for all patients.

Some gene mutations cause severe disease in CGD patients, and in study conducted in Jordan included seven Libyan patients with CGD, underwent genetic testing, all of the Libyan CGD patients had defect in CYBA gene, which is one type of AR-CGD and leads to severe form of CGD with early presentation, and this is another reason that may explain the increase in frequency of infections and mortality in our study (9,35). In conclusion, this is the largest study conducted in Libya included 54 CGD patients, and it revealed severe clinical course with increase in mortality in our patients. Therefore, increase in the awareness among doctors about the characteristic clinical presentation of CGD is important for early diagnosis and treatment.

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