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Chronic Granulomatous Disease in Libya:

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Abstract:
Chronic granulomatous disease (CGD) is a rare inherited disorder of the innate immune system, characterized by a greatly increased susceptibility to severe infections, early in childhood at different sites. We aimed to study multisystem clinical manifestations of CGD in Libyan children. Our study was retrospective, it included CGD patients seen at Pediatric hospital immunology department in Benghazi, over 7 years. Out of 35 CGD patients, 66% was males, 94% had onset of disease <1 year of life, and 60% of their parents were relatives. Reticuloendothelial system was involved in 94% followed by skin (91%), respiratory (83%), gastrointestine (69%) and bone (29%). This study is one of the largest series on CGD from north Africa and Arabic region reflecting the different modes of inheritance, as well as the wide and variable clinical manifestations of CGD.

I. Introduction and objectives:

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disease, characterized by failure to activate the respiratory burst in the phagocytes. It is inherited as autosomal recessive (AR) or x-linked recessive trait. Patients with CGD have a greatly increased susceptibility to recurrent life-threatening infections early in childhood at different sites. Prolonged dysregulated inflammatory reactions may produce granulomatous lesions.(1)We aimed to study CGD in Libyan children, to evaluate the diverse multisystem clinical manifestations of CGD and their prevalence.

II. Methods & Materials:

Our study was retrospective, we used data from primary immunodeficiency registry in immunology department at Pediatric hospital in Benghazi, Libya.
It included all CGD pediatric patientspresented between 2007 and 2013.Their diagnosis was based on clinical features and confirmed by Nitroblue Tetrazolium (NBT) test.Sex, age, age at onset, family history, and consanguinity were recorded. Clinical features and laboratory investigations were recorded.

III. Results:

We reviewed the records of 35 patients, 23 males and 12 females(Figure 1), 94% had onset of their disease before the first year of life (Figure 2), 63% had positive family history (Figure 3)and 60% of their parents were relatives. Reticuloendothelial system was the most commonly involved system (94%) followed by skin (91%) and respiratory (83%) (Figure 4). Hepatosplenomegaly was reported in 91%,suppurative lymphadenitis in 80%, whereas liver and spleen abscess in17% and 6% respectively. Skin abscesses was seen in 75%, perianal abscesses and fistulas in one third, BCGitis (20%), granuloma (14%) and tinea corporis (6%).Pneumonia was the main respiratory problem (83%), aspergillosis (23%), bronchiectasis (14%) and pulmonary abscess in 6%. Anemia was seen in 83% followed by hypergammaglobulinemia (63%), thrombocytosis (51%) and leukocytosis

(46%). GIT was involved in 69% and oral findings in 49%. Osteomyelitishad occurred in 29%, meningitis in 6%, and sepsis in 46%. Forty two had failure to thrive.
(Figures 5–12 show variable CGD presentations)

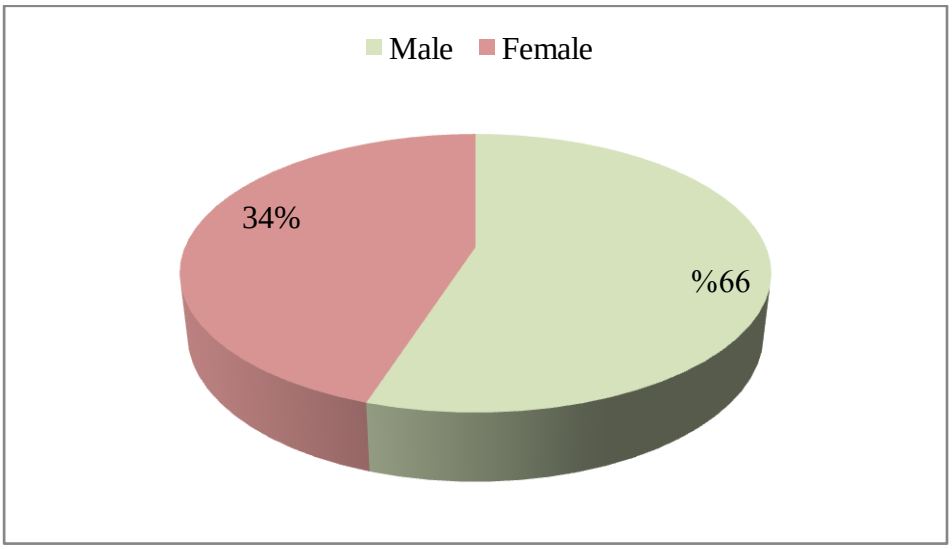


Figure 1: Sex distribution

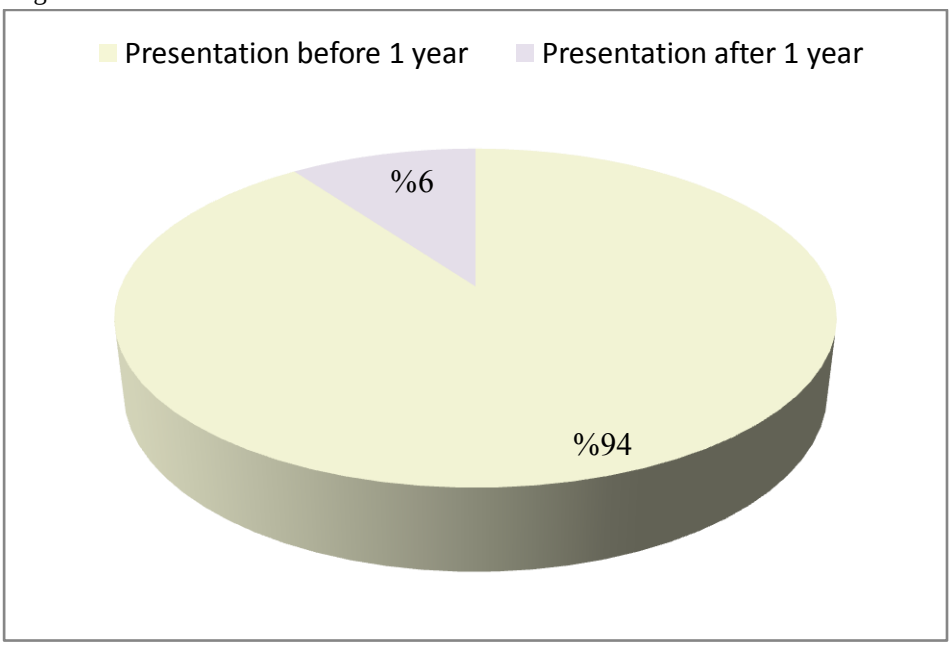


Figure 2: Presentation age

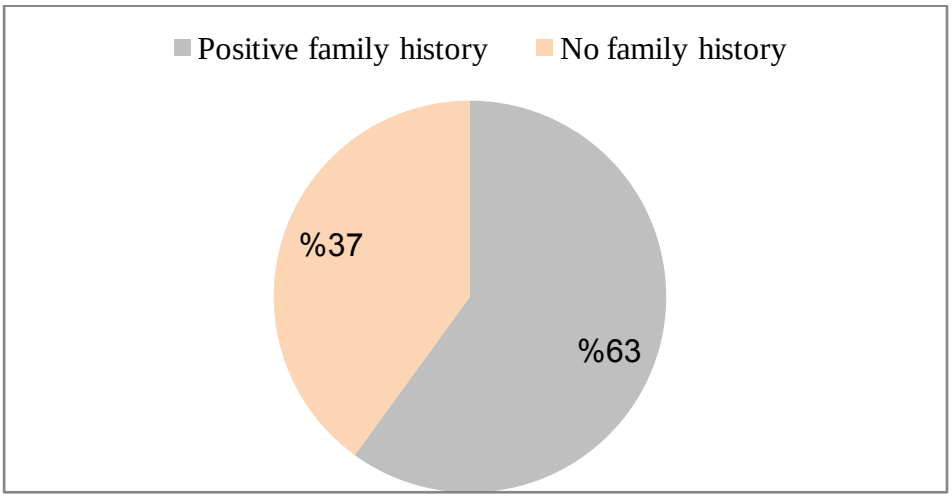


Figure 3: Family history among CGD

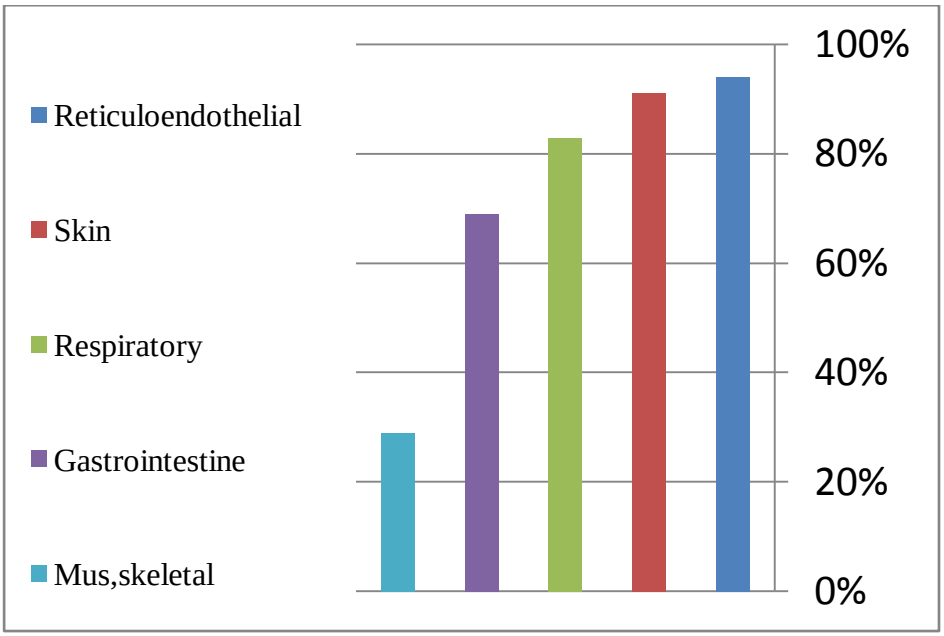


Figure 4: Multisystem clinical manifestations of CGD

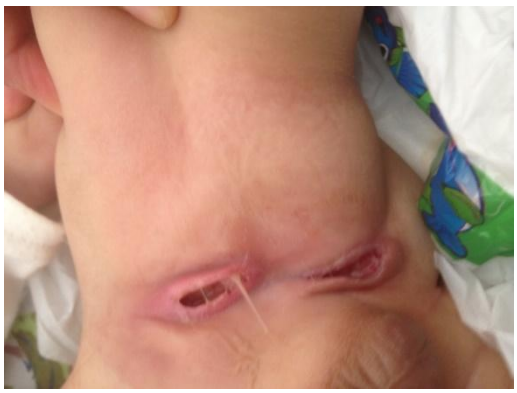


Figure 5: Suppurative lymphadenitis

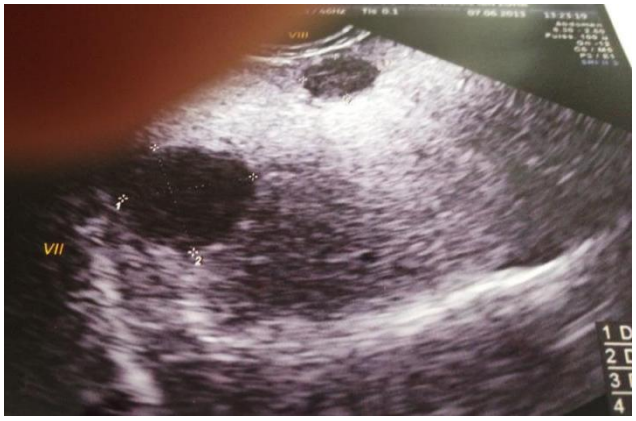
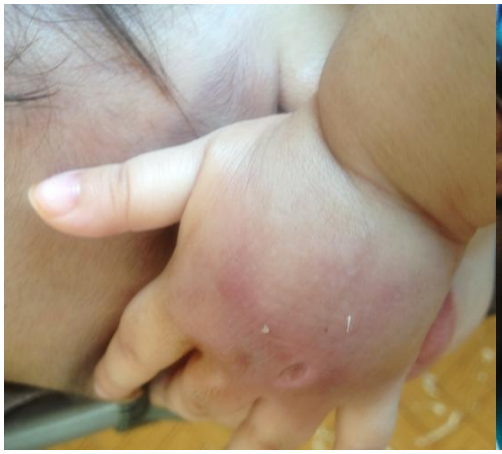


Figure 6: Spleen abscess



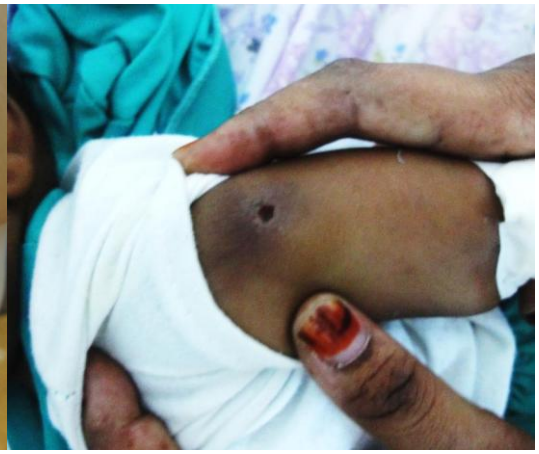


Figure 7: Skin abscessesFigure 8: BCGitis

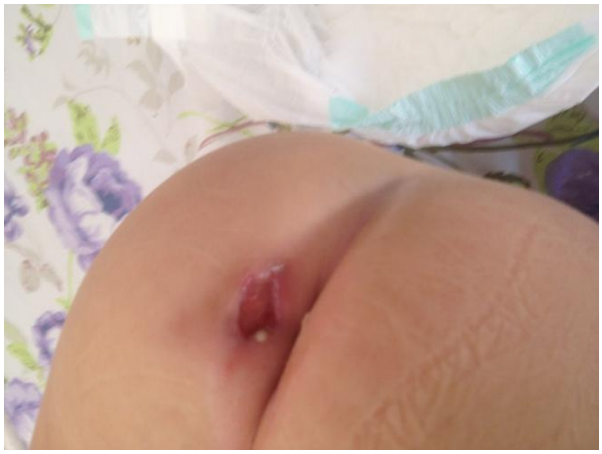


Figure 9: Perianal abscess

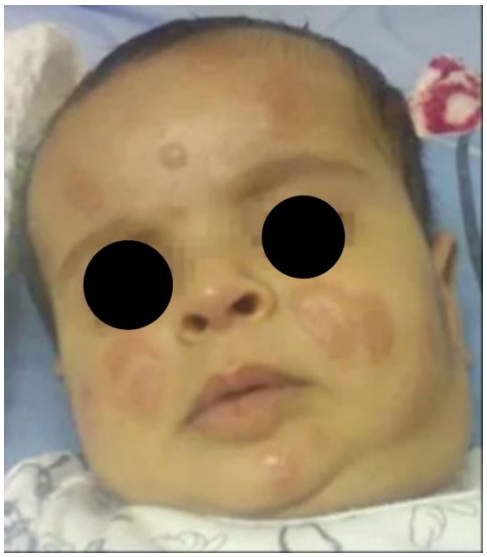
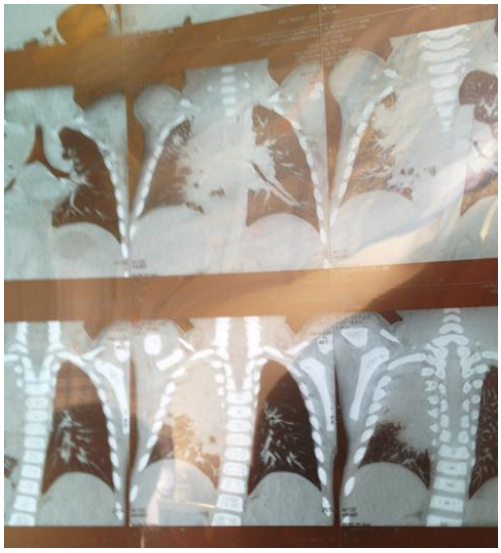


Figure 10: Skin granuloma



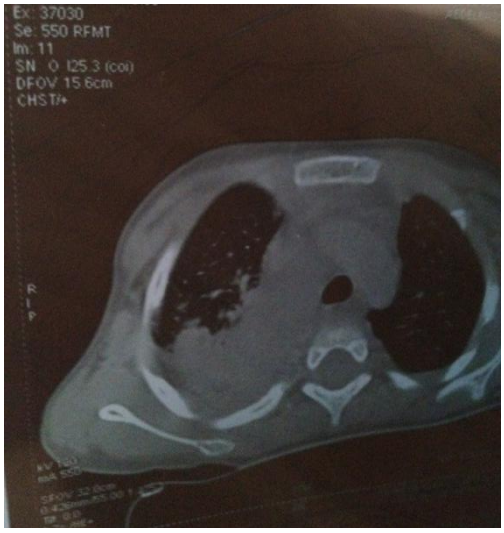


Figure 11a: PneumoniaFigure 11b: Pneumonia

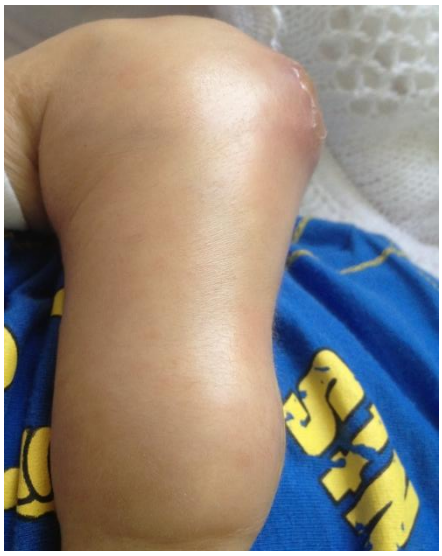
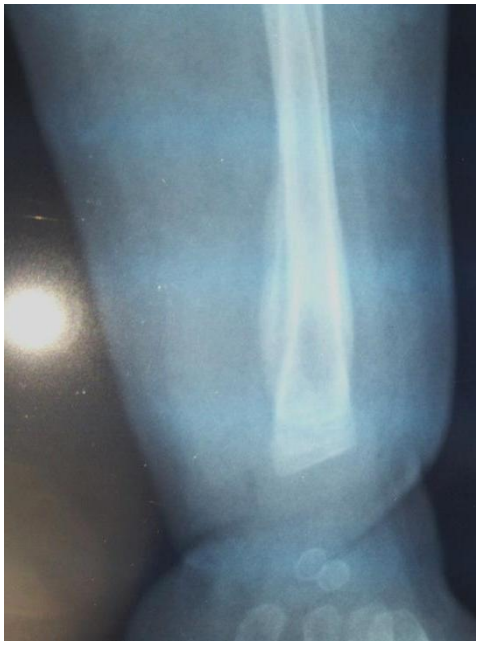



Figure 12a: Osteomylitis (clinical)Figure 12b: Osteomylitis (radiological)

IV. Discussions:

CGD is caused by mutations in genes that encode the phagocyte nicotinamide dinucleotide phosphate oxidase, the enzyme that generates microbicidal oxygen radicals, such as H2O2 and hydroxyl anion.(2 , 3)Leukocytes ingest bacteria but do not kill them. The intracellular survival of ingested bacteria leads to the development of granuloma in the lymph nodes, skin, lungs, liver, GITand bones.

Most infections in CGDare caused by Staphylococcus aureus, Psedomonas species, Serratiamarcescens and fungi including Aspergillus species and Candida albicans.(4)

In this study 35CGD patients were reported over 7 years in a single center covering north eastern Libya, our data was higher than the reported in a Moroccan study.(5)

CGD is inherited as an x-linked recessive or as AR. X-linked disease is the most common type in the western countries whereas AR form was more common in middle east countries as a result of increased consanguineous marriages.(6)Pedigree of our CGDpatients reflected both inheritance.

The disease is usually diagnosed in childhood and sometimes in early adulthood,(4)94%of our CGD patients had onset of their disease before the first year of life consisting with other studies.(7)CGD presents most often with infections commonly involved organs are those that serve as barriers against the entry of microorganisms from the environment, including the skin, lungs, GIT.(1)Our data was compatible with Winkelstein and coworkers report on the United States CGD experience.(4)

Suppurative lymphadenitis, hepatosplenomegaly and spleen or liver abscesses are common initial manifestations. In this study 91% had hepatosplenomegaly and 80% suffered from suppurative lymphadenitis.

Pneumonia is often the most common complication. It may lead to abscess formation, cavitation, and empyema. (8-10) Pneumonia was the main respiratory problem in our patients (83%).

Skin manifestations in CGD include recurrent furuncles and subcutaneousabscess; commonly perianalabscess, eczema, and granuloma.Abscesses characteristically heal slowly.Scars secondary to multiple surgical procedures are characteristically seen.Skin complications were seen in 91% with the skin abscesses was seen in three quarters and perianal abscesses and fistulas in one third.

GITinvolvement include oral ulcerations, chronic gingivitis and granulomatous colitis.(11-13)It was involved in 69% with oral findings was present in nearly half of our patients.

CGD have several skeletal complications, mainly related to infections. Osteomyelitis may involve long bones or spine, it is particularly caused by Aspergillusspecies.(4)Osteomyelitis had occurred in nearly one third of our patients.

Patients with CGD can develop neurological complications including meningitis, brain abscess and granuloma, (4) in this study meningitis was reported in 6%.
CGD clinical and laboratory abnormalities often suggest the diagnosis. The confirmatory test is measurement of the oxidative burst of the neutrophil in response to stimulation (NBT). Molecular mutational analysis can confirm the diagnosis.(4,12,13)

V. Conclusions:

This study is one of the largest series on CGD from north Africa and Arabic region reflecting the different modes of inheritance, as well as the wide and variable clinical manifestations of CGD. Reticuloendothelial, cutaneous and respiratory manifestations were the most prevalent. Awareness of CGD features may aide in the early detection and management of this serious life-threatening disease.

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