Mycobacterial disease in patients with chronic granulomatous disease: A retrospective analysis of 71 cases

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Background: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency caused by inborn errors of the phagocyte nicotinamide adenine dinucleotide phosphate oxidase complex. From the first year of life onward, most affected patients display multiple, severe, and recurrent infections caused by bacteria and fungi. Mycobacterial infections have also been reported in some patients.

Objective: Our objective was to assess the effect of mycobacterial disease in patients with CGD.

Methods: We analyzed retrospectively the clinical features of mycobacterial disease in 71 patients with CGD. Tuberculosis and BCG disease were diagnosed on the basis of microbiological, pathological, and/or clinical criteria.

Results: Thirty-one (44%) patients had tuberculosis, and 53 (75%) presented with adverse effects of BCG vaccination; 13 (18%) had both tuberculosis and BCG infections. None of these patients displayed clinical disease caused by environmental mycobacteria, *Mycobacterium leprae*, or *Mycobacterium ulcerans*. Most patients (76%) also had other pyogenic and fungal infections, but 24% presented solely with mycobacterial disease. Most patients presented a single localized episode of mycobacterial disease (37%), but recurrence (18%), disseminated disease (27%), and even death (18%) were also observed. One common feature in these patients was an early age at presentation for BCG disease. Mycobacterial disease was the first clinical manifestation of CGD in 60% of these patients.

Conclusion: Mycobacterial disease is relatively common in patients with CGD living in countries in which tuberculosis is endemic, BCG vaccine is mandatory, or both. Adverse reactions to BCG and severe forms of tuberculosis should lead to a suspicion of CGD. BCG vaccine is contraindicated in patients with CGD. (J Allergy Clin Immunol 2016;138:241-8.)

Key words: *Mycobacteria, BCG, chronic granulomatous disease, tuberculosis, primary immunodeficiency*

Chronic granulomatous disease (CGD) is a primary immunodeficiency (PID) characterized by the production of reactive oxygen species in small amounts, if at all, by phagocytes because of a deficiency of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[1-3] The phagocyte NADPH oxidase is an enzymatic complex composed of a membrane-bound core, the heterodimeric flavocytochrome, consisting of gp91^{phox} (encoded by *CYBB*) and p22^{phox} *(CYBA)*, and the cytosolic subunits p47^{phox} *(NCF1)*, p67^{phox} *(NCF2)*, and p40^{phox} *(NCF4)*. Mutations in any of the 5 genes (*CYBB*, *CYBA*, *NCF1*, *NCF2*, and *NCF4*) encoding the membrane-bound or cytosolic components of the phagocyte NADPH oxidase are responsible for CGD.[4-7]

Affected patients experience severe and recurrent infections caused by a diverse but relatively specific set of bacteria and fungi and from uncontrolled inflammation that can lead to granuloma

Abbreviations used
AR: Autosomal recessive
CGD: Chronic granulomatous disease
EM: Environmental mycobacteria
MSMD: Mendelian susceptibility to mycobacterial disease
NADPH: Nicotinamide adenine dinucleotide phosphate
PID: Primary immunodeficiency
XR: X-linked recessive

formation.[3,8] The main infections observed in patients with CGD are pneumonia, skin lesions, liver abscesses, and osteomyelitis. The most commonly isolated pathogens are *Aspergillus*, *Burkholderia*, *Nocardia*, and *Staphylococcus* species,[9] but gram-negative extracellular bacteria, such as *Serratia* species,[1] and other fungi, such as *Scedosporium* species,[10] are also frequently identified. Mycobacterial infections are not negligible among the pathogens causing infectious diseases in patients with CGD, especially in countries in which BCG vaccine is routinely administered, tuberculosis is endemic, or both.[11]

In a review of the literature, Deffert et al[12] reported a total of 297 cases of mycobacterial infections in patients with CGD.[13-24] BCG disease has been reported in 220 (74%) patients with CGD.[11] Similarly, tuberculosis has been reported in 59 (20%) patients.[11] Disease caused by environmental mycobacteria (EM) or unidentified species was reported in 18 (6%) patients.[12,25-33] However, the clinical features of mycobacterial disease remain poorly described. We examine the clinical manifestations of mycobacterial disease in 71 patients with CGD from 20 countries on 4 continents.

METHODS

Subjects and kindreds

Patients with CGD were recruited retrospectively for this study through extensive collaboration with clinicians in Latin America, Africa, Europe, and Asia, particularly in regions and countries in which tuberculosis is endemic and BCG vaccination is routine.[10] These patients were referred to the laboratory of human infectious diseases because of mycobacterial infections, and therefore they might not be representative of the entire CGD population. Informed consent forms were signed by the parents, as requested and approved by the institutional review boards of the various institutions involved. Data were collected from 2007 to 2013 and sent to Dr Bustamante.

A detailed questionnaire was completed by the physicians, including demographic data (age, sex, and country), biological tests for CGD diagnosis, mutations (where available), and infectious diseases. CGD was diagnosed on clinical grounds and confirmed with at least 1 of 3 laboratory tests,[34] the nitroblue tetrazolium reduction assay, dihydrorhodamine 123 oxidation, and/or superoxide production (cytochrome c reduction) assay, on whole-blood samples and/or EBV-transformed lymphoblastoid cell lines. Our analysis focused exclusively on mycobacterial infectious disease in patients with CGD and did not take into account other clinical signs. This constitutes one of the limitations of this retrospective study. Mycobacterial infections were diagnosed on the basis of clinical and radiologic findings, staining for acid-fast bacilli, supportive histology, serology (ELISA), and molecular (PCR) findings and microbiological culture results, when available.

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