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**“DETECTION OF INHERITANCE PATTERN IN  
THIRTY THREE MEXICAN MALES WITH  
CHRONIC GRANULOMATOUS DISEASE THROUGH  
123 DIHIDRORODAMINE ASSAY”**

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MEXICAN MALES WITH CHRONIC GRANULOMATOUS DISEASE  
THROUGH 123 DIHIDRORODAMINE ASSAY"**

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## **ABSTRACT**

*BACKGROUND* There are two inheritance patterns, the X-linked recessive (XL) pattern and the autosomal recessive pattern. There is no information on the predominant inheritance pattern of male patients with chronic granulomatous disease (CGD) in Mexico.

*OBJETIVE* The aim of this study was to determine the inheritance pattern in a cohort of Mexican male patients with CGD by means of the detection of an XL status carrier among their female relatives, and to describe the frequency of discoid lupus (DL) among carriers.

*METHODS* We detected the female relatives within the families of male patients with CGD, and carried out the 123-dihydrorhodamine (DHR) assay for all female participants. All carriers were questioned for current or past established DL diagnosis.

*RESULTS* We detected 33 families with one or more CGD male patients; we found an XL-CGD in 79% of the kindred from at least one female relative with a bimodal pattern. For the remaining seven kindred we were not able to confirm a carrier status by means of a DHR assay. Moreover, we detected one mother with CGD secondary to skewed X-chromosome inactivation. We also found 47 carriers, and only one carrier with DL among them.

*CONCLUSION* We concluded that XL-CGD is the most frequent form of CGD in a cohort of CGD male patients in Mexico. DHR assay is a fast and practical tool to determine the CGD form in the Latin-American countries. Finally, DL frequency in Mexico is lower than that reported in the literature for other regions of the world.

## INTRODUCTION

Chronic Granulomatous Disease is the most commonly encountered immunodeficiency involving the phagocyte, and is characterized by repeated infections with bacterial and fungal pathogens, as well as the formation of granulomas in tissue. The disease is the result of a disorder of the NADPH oxidase system, culminating in an inability of the phagocyte to generate superoxide, leading to the defective killing of pathogenic organisms. This can lead to infections with *Staphylococcus aureus*, *Pseudomonas* species, *Nocardia* species, and fungi (such as *Aspergillus* species and *Candida albicans*).

It is known from the patient registries of chronic granulomatous disease from several countries that the frequency is about 1 in 200,000 in the general population. In the registry in the United States, about 75% of patients have the X-linked form of chronic granulomatous disease, which involves mutations of the gp91phox gene present on the X chromosome. About 20% of patients have autosomal recessive chronic granulomatous disease resulting from mutations in the p47phox gene present on chromosome 7. Three percent and 2% of patients, respectively, have autosomal recessive disease resulting from mutations in either p67phox (chromosome 1) or p22phox (chromosome 16). Registry survival data indicates that patients with X-linked chronic granulomatous disease have a higher rate of infections and higher mortality (about 3–5% rate of death per year) than the p47phox-deficient autosomal recessive patients (about a 1–2% rate of death per year). Although an extraordinarily rare immune deficiency/recurrent infection syndrome associated with an inherited abnormality of Rac-2 (a heterozygous dominant-negative effect mutation) has been described, the disease phenotype does not resemble chronic granulomatous disease (there are no granulomas) and the primary defect at the cellular level is a defect in neutrophil movement with only a mild defect in oxidase activity. No patient with a disease process attributed to a primary deficiency of the p40phox subunit of the oxidase has been reported.

The mean age at diagnosis of X-linked chronic granulomatous disease is about 3 years of age, whereas male and female autosomal recessive patients are on average not diagnosed until over 7 or 8 years of age, respectively. Some patients, particularly those with p47phox autosomal recessive chronic granulomatous disease, may reach adulthood without a diagnosis being made. Thus, an adult without a known predisposing factor who has a type of infection that is unusual in the general population, but typical of chronic granulomatous

disease (e.g., *Burkholderia cepacia* or other *Burkholderia* species pneumonia, *Aspergillus* pneumonia, staphylococcal liver abscess, *Serratia marcescens* soft tissue or bone infection), should have specific testing for chronic granulomatous disease.

Chronic Granulomatose Disease (CGD) is a primary immunodeficiency, caused by a complete lack of or significant decrease in production of microbicidal reactive oxygen metabolites. CGD is caused by a defect in any one of four components of NADPHoxidase. Mutations in gp91phox gene (CYBB on Xp 21.1) cause the X-linked recessive form of the disease that affects about 70% of all CGD patients. As expected from the genetics, the overwhelming majority of X-linked patients are male. The remaining 30% of cases are inherited in autosomal recessive (AR-CGD) manner in which males and females are equally affected. Individuals with X-CGD have a more severe clinical phenotype and increase in mortality than those with AR-CGD.(Goldblatt and Thrasher 2000) .

An often fatal first presentation of p47phox-deficient autosomal recessive chronic granulomatous disease in teenagers or adults is an inhalation-related acute miliary aspergillosis that shares many of the features of allergic bronchopulmonary aspergillosis (ABPA). Although both syndromes may occur following an acute exposure to aerosolized *Aspergillus* spores (spreading garden mulch is the most common exposure), and are associated with patchy or miliary pulmonary infiltrates and a hypoxia that is very responsive to steroid administration, ABPA does not require systemic antifungal therapy, whereas the inhalation-related acute miliary aspergillosis infection in a patient with chronic granulomatous disease will initially appear to respond to steroids alone, but will then progress to death of the patient without administration of systemic antifungal antibiotics (agents with potent anti-*Aspergillus* activity that include voriconazole, candidacidins, intravenous itraconazole, and amphotericin B preparations, but not fluconazole). The diagnosis and treatment of this syndrome are discussed in more detail later.

Soft tissue infection or osteomyelitis with *Serratia* is the most common presentation in infants (<1 year old). Lung, lymph node, bone, or skin infection with *Burkholderia* bacterial species, *Nocardia*, or *Aspergillus* is a common presentation leading to the diagnosis of chronic granulomatous disease in older children or adults. Liver abscess with *Staphylococcus aureus* is a less common initial presentation. Patients with chronic granulomatous disease are more susceptible than normal to tuberculosis, and, in countries with a high endemic rate of tuberculosis (e.g., India and China), a severe infection with tuberculosis may be the



presenting infection in a child with chronic granulomatous disease. In countries with a low endemic incidence of tuberculosis, such as western Europe, the United States, and Japan, tuberculosis in patients with chronic granulomatous disease is uncommon. However, the microgranulomas associated with chronic granulomatous disease can at times be similar enough to those seen in tuberculosis that many patients, before their diagnosis of chronic granulomatous disease is discovered, may be told that they have a "culture-negative" tuberculosis and are actually treated for it. Later, when the diagnosis of chronic granulomatous disease is made, their medical records continue to carry a diagnosis of tuberculosis, but in most cases a review of their old records suggests that this was a misdiagnosis.

Although other presentations are common with chronic granulomatous disease, these other presentations do not in themselves usually lead to this diagnosis. Chronic granulomatous disease may be associated with unexplained partial gastric outlet obstruction or unexplained ureteral or bladder outlet obstruction without stone in a child. A large bladder granuloma can present as a "pseudotumor" (mistakenly misdiagnosed as a cancer until histology shows granuloma formation). Chronic granulomatous disease is a rare cause of a syndrome indistinguishable from Crohn's disease; in fact, at some time in their lives at least 20% of patients with chronic granulomatous disease have gastrointestinal granuloma problems that may include chronic abdominal pain and/or bloody diarrhea. In some cases, such as older teenagers or young adults with the p47phox autosomal recessive form of chronic granulomatous disease, who have a lower incidence of infections than do patients with the X-linked form, the lower gastrointestinal colitis may be their primary or only problem.

X-chromosomal lyonization explains that there is a random inactivation of one X-chromosome in somatic cells early in fetal development. This results in two distinct populations of polymorphonuclear leucocytes, one with normal production and other with abnormal production of microbicidal reactive oxygen metabolites in a carrier. The two populations could be detected through DHR assay, it shown a bimodal histogram in the carriers. (Bakri, Martel et al. 2009).

Based on several clinical studies, chronic granulomatous disease patients in the United States are routinely placed on a prophylactic infection prevention regimen consisting of the following medications:

1. Daily oral trimethoprim-sulfamethoxazole (co- trimoxazole: about 4.6mg/kg/day trimethoprim and 22.8mg/kg/day sulfamethoxazole for bacterial prophylaxis)

2. Daily oral itraconazole (about 4–5mg/kg/day for fungal prophylaxis)
3. Three-times-weekly subcutaneous injections of recombinant interferon gamma (50µg/m<sup>2</sup> surface area)

Allogeneic bone marrow or other hematopoietic stem cell transplantation represents the only current treatment capable of permanently curing chronic granulomatous disease by replacing the oxidase-deficient neutrophils, monocytes, and tissue macrophages with donor cells produced from marrow that have normal oxidase activity. As noted earlier, the outlook for survival and long periods of normal infection-free living for chronic granulomatous disease patients has greatly improved and continues to improve. This has resulted from effective prophylactic regimens (trimethoprim-sulfamethoxazole, itraconazole, interferon gamma, low-dose alternate-day steroids where necessary for granuloma control); aggressive approaches to infection diagnosis (computed tomography, magnetic resonance imaging, needle biopsy); improvements in antibiotics (particularly the availability of voriconazole, a potent oral antifungal alternative to intravenous amphotericin B, and linezolid, a potent oral anti-staphylococcal agent); and early recognition of specific types of infections and granuloma/inflammation syndromes and the proper treatment of these problems. However, significant improvements have also occurred in bone marrow transplantation, which include better molecular matching of donor to recipient, improved agents and methods for marrow and immune suppression conditioning, improvements in agents and methods to detect and treat transplant-associated infection, and improvements in agents and methods to prevent or treat acute and chronic graft-versus-host disease. Thus, the risk-benefit ratio of allogeneic stem cell transplantation for chronic granulomatous disease is changing, and currently it is difficult to make blanket statements about the role of allogeneic stem cell transplantation in the management of chronic granulomatous disease.

Chronic granulomatous disease patients most at risk are those with the completely oxidase-negative X-linked form, and that subset of patients of any genetic sub-type who have a sustained history of recurrent life-threatening infections. The lowest morbidity and mortality from allogeneic stem cell transplantation is seen in children with a fully human lymphocyte antigen-matched sibling donor. Thus, a consensus is beginning to emerge that chronic granulomatous disease patients at highest risk who have such a donor should be considered for allogeneic transplantation. Although experimental nonablative marrow conditioning regimens can reduce morbidity and make possible the consideration of transplantation in a

chronic granulomatous disease patient who has an incurable and otherwise fatal infection, experimental nonablative conditioning regimens have been reported to be associated with a significantly higher rate of graft failure, particularly in children. Therefore, in a patient with chronic granulomatous disease considered for matched sibling donor transplantation who is not actively infected at the time of transplantation, the current consensus appears to favor more conventional marrow conditioning regimens. There may be a place for matched unrelated transplants, including unrelated cord blood transplants, in a specific patient based on infection history, but such transplants carry significantly higher risk of morbidity, mortality, and graft failure, and must be considered experimental.

The objective of this study was identified the inheritance pattern in the 30 Mexican males with CGD through the finding of a carrier in their female relatives with DHR assay. Also we determined the presence of discoid lupus in the carriers and offered them genetic counseling.

## PATIENTS AND METHODS

### *Patients*

The parents with one or more male patients with CGD without a determined inheritance pattern, from eight different hospitals along Mexico were invited to participate in our study. Firstly we performed the family tree to identify all the female relatives from maternal branch, after we invited them to participate in the study. The protocol was reviewed and approved by the appropriate local Ethics and Research Committees in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The participants who accepted to participate signed the informed consent and/ or the informed assent. All carriers were interrogated if they had a currently or past diagnosis of discoid lupus established by a physician. Also the genetic counseling was offered to all carriers.

Three milliliters of venous blood were obtained from each participant and collected in lithium heparin vacutainers tubes.

### *Materials and Methods:*

The working dilution of Dihydrorhodamine 123 (DHR 123)(45µg/ml) was prepared adding 30µl of DHR to the ((DHR; Molecular Probes, Eugene, OR.)) stock solution (5 mg/ml) to 3.33 ml of phosphate-buffered saline (PBS). To prepare working dilution of Phorbol-myristate-acetate (PMA)(10µL) we added 10 µL of PMA (Sigma Chemical, Munich, Germany) stock (1 mg/ml) to 1 ml of PBS.

### *Dihydrorhodamine flow cytometry assay*

Three 100 µl samples were taken from each whole blood of the possible carrier and placed in separate tubes. These were used as stimulated (1), resting (2) and reagent blank tests (3). Twenty-five µl working DHR solution (final concentration 1.125 µg/ml) was added to the stimulated (1) and resting samples (2). All tubes were incubated at 37°C for 15 min. Then 10 µl of PMA solution (final concentration 100 ng/ml) were added to the stimulated tubes(3). After further 20 min incubation at 37°C, 1.0 ml FACS lysing solution (Becton Dickinson, Heidelberg, Germany) were added to all tubes. The tubes were left at room temperature for 20 min and

then centrifugated. The supernatant was discarded and the cells were washed twice with 2 ml of PBS. After the second centrifugation, the supernatant was discarded and replaced with 0.25 ml of 1% paraformaldehyde.

By using the FACSARIAS I® (Becton Dickinson, Heidelberg, Germany) non-fluorescent parameters (forward and side scatter) were collected, as well as FL2. 20 000 events were acquired in the established granulocyte gate for each tube. Data analysis was performed using FlowJo 7.2.4 software (Tree Star. Inc, Ashland, OR, USA). Calculate the normal oxidative index (NOI) by dividing the mean fluorescence of stimulated tube by the mean fluorescence obtained in resting tube. A carrier status for X-linked CGD was defined as a woman with a bimodal histogram pattern in the DHR assay (fig 2).

Figure 1. Control vs Carrier status

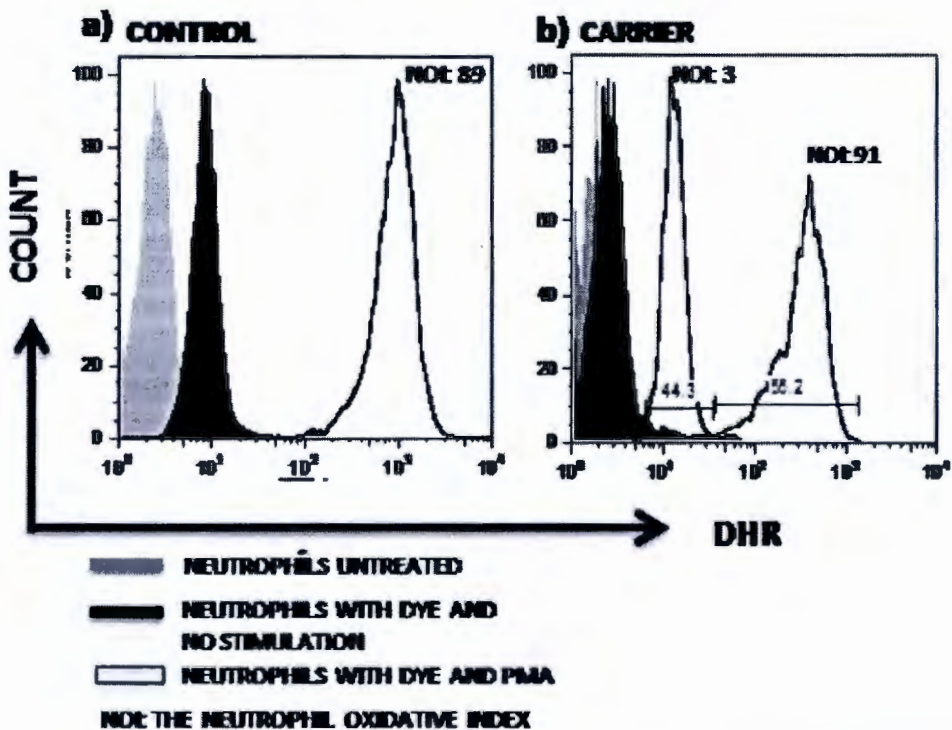


Figure. 1 In the left panel, typical DHR histogram and NOI in a normal subject, in right panel, DHR histogram and NOI in a CGDXL carrier.

Figure 2. Carrier status.

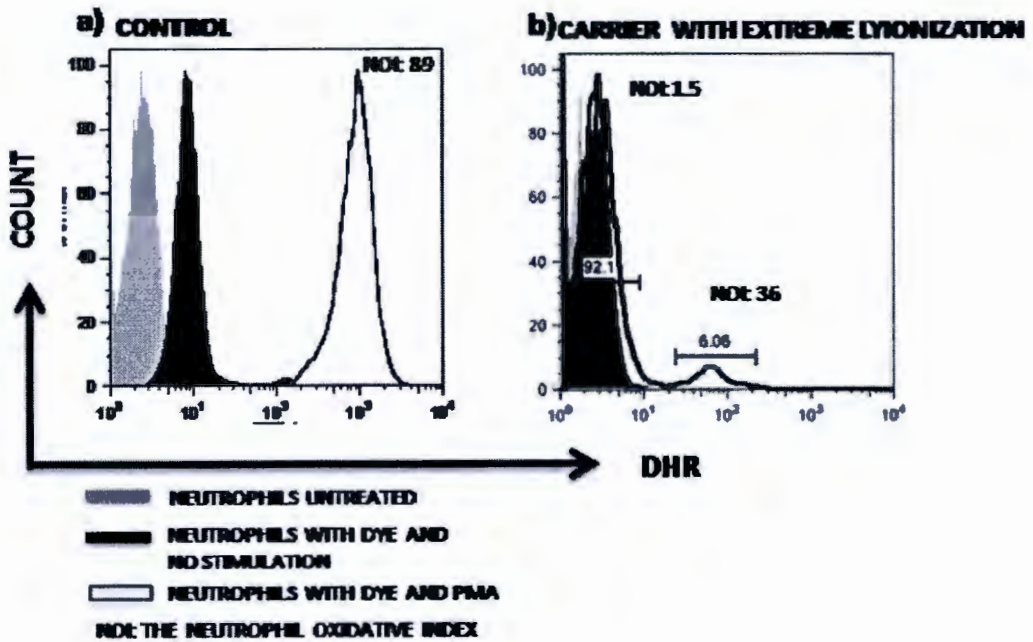


Figure. 2 In the *left panel*, typical DHR histogram and NOI in a normal subject, in *right panel*, DHR histogram and NOI in a carrier with extreme lyonization.

## RESULTS

Over the period from November 2010 to October 2012 we detected 33 families with at least one male with CGD. We tested with DHR assay ninety women. In twenty six (79%) kindred we determined an X-linked inheritance pattern through at least one female with a bimodal pattern. In the remaining seven kindred we could not confirm through DHR assay any carrier status.

We found in all the 26 kindred with the X-linked inheritance pattern CGD a total of 47 carriers, among them 26 mothers, 8 sisters, 8 grandmothers, 3 aunts, 1 cousin, and 1 niece (Table 1). In 16 kindred the grandmother as well as the mother was tested with DHR assay, 8 grandmothers had a bimodal pattern and therefore a carrier status. In the remainders 8 grandmothers we did not find any carrier neither in their others members of family different to the mother or/and the sister of the patient.

In the family 11, the mother of a death CGD boy participated, she and her daughter had histogram bimodal pattern.

We found in the family 17 that the mother had a CGD secondary to skewed X-chromosome inactivation, DHR assay showed only 5.3% functional neutrophils. (fig #). At the study, she was 30 years old, she had a history of recurrent episodes of cervical suppurative lymphadenopathies and a liver abscess after 15 years old, and previously she was healthy. Also her daughter resulted as a carrier. Her mother and her five sisters had a normal pattern on DHR test.

Of the total 46 carriers only one (2.21%) suffered discoid lupus in the third decade of life (family 15).

**Table 1.**

46 carriers in 26 families with X-linked CGD inheritance pattern detected through 123-DHR.

Family code	Carriers and their relationship with the patient	The affected offspring	Grandmother DHR status	Others findings
1	MOTHER	2 ALIVE CGD PATIENTS	carrier	
	GRANDMOTHER	1 DECESED BOY AT 1 YEAR OLD		
2	MOTHER	1 ALIVE CGD PATIENT, ONE DECEDES BOY	carrier	
	GRANDMOTHER	¿?????????		
3	MOTHER	1 DECEDED CGD PATIENT 1 ALIVE CGD PATIENT	Not done	
4	MOTHER	1 ALIVE CGD PATIENT	carrier	
	GRANDMOTHER			
5	MOTHER	1 ALIVED CGD PATIENT	carrier	
	GRANDMOTHER	1 DECESED BOY AT 6 MONTHS OLD SECONDARY TO MENINGITIS		
6	MOTHER	1 ALIVE CGD PATIENT	No carrier	
	SISTER	*		
7	MOTHER	1 ALIVE CGD PATIENT	Not done	
8	MOTHER	1 ALIVE CGD PATIENT	Not done	
9	MOTHER	1 ALIVE CGD PATIENT	No carrier	
	SISTER	*		
10	MOTHER	2 DESCESED CGD PATIENTS, 1 ALIVE CGD PATIENT	Not done	Mc Leod syndrome
11	MOTHER	1 DESCESED CGD PATIENT	No carrier	Postmortem detection of X-linked inheritance pattern
	SISTER	*		
12	MOTHER	1 ALIVE CGD PATIENT	Not done	
13	MOTHER	1 ALIVE CGD PATIENT	Not done	
14	MOTHER	1 ALIVE CGD PATIENT	Non carrier	
	SISTER	**		
	NIECE	*		



15	MOTHER	1 ALIVE CGD PATIENT	carrier	The mother of the patient suffered discoid lupus
	GRANDMOTHER	1 DESCESED BOY AT 3 MOTHS SECONDARY TO INFECTION		
	AUNT	***		
16	GRAN MOTHER	1 DESCESED CGD PATIENT 1 ALIVE CGD PATIENT	carrier	
	MOTHER	1 DESCESED CGD PATIENT		
	AUNT	**		
17	MOTHER	1 ALIVE CGD PATIENT	No carrier	The mother had a CGD secondary to skewed X-chromosome inactivation
	SISTER	*		
18	GRANDMOTHER	1 ALIVE CGD PATIENT	carrier	
	MOTHER	1 ALIVE CGD PATIENT		
	COUSIN	***		
	AUNT	**		
19	MOTHER	1 ALIVE CGD PATIENT	Not done	
	SISTER	*		
	SISTER	*		
20	MOTHER	1 ALIVE CGD PATIENT 1 DESCED CGD PATIENT	Not done	
21	MOTHER	2 ALIVE CGD PATIENTS	Not carrier	
22	MOTHER	2 ALIVE CGD PATIENTS	Not carri	
23	MOTHER	1 ALIVE CGD PATIENTS	Not done	
24	GRANDMOTHER		carrier	
	MOTHER	1 ALIVE CGD PATIENTS		
25	MOTHER	1 DESCESED CGD PATIENT	Not done	
	SISTER	*		
26	MOTHER	1 ALIVE CGD PATIENT	Not carrier	

\*Young girl, without descendant. \*\* Female descendant. \*\*\* Woman, without descendant.

## DISCUSSION

X-linked CGD is the inheritance pattern most prevalent around the world; in a cohort of 33 Mexican families we found at least in 26 (79%) families an X-linked pattern, in the six remaining we cannot conclude X-CGD or CGD-AR through DHR assay, because of in case of skewed X-chromosome inactivation, all cells will be positive for DHR oxidation and therefore a bimodal histogram pattern will not be seen in the DHR assay in a carrier. In this case the additional study of sisters, grandmother or nephews could reveal a bimodal histogram pattern. HUMARA analysis is needed to rule out lyonization defect or not in the mother. A second possibility if the mother doesn't have a bimodal pattern is *novo* mutation in *CYBB* gene in the patient or in the mother germinal cells. The third possibility and most probably is an AR-CGD in which the carrier has a normal histogram and diagnosis must be confirmed through the molecular study.(Anderson-Cohen, Holland et al. 2003; Chollet-Martin, Lopez et al. 2007; Lewis, Singla et al. 2008).

Other practical advantage of DHR assay in the female relatives in our study was the determination of an X-linked pattern in a deceased CGD male. We detected retrospectively a carrier status in the mother and sister (family 11) and could offer a genetic counseling. (Lakshman, Bruce et al. 2005)

In the 17 family we found that DHR assay in the mother had a pattern compatible with CGD, also the sister was carrier. We concluded that the mother had an extremely skewed X chromosome inactivation. The inactivation of the X-chromosome in the carriers has given different proportion of positive and negative cells depending on what X chromosome is preferentially inactivated, providing from normal to pathological results .(Segal, Leto et al. 2000). Thus an advantage of DHR assay performance in patient and mother at par is the detection of a skewed X chromosome inactivation. The grandmother and the aunts were normal in DHR which suggest a *novo* mutation in mother *CYBB* gene, molecular study is the confirmatory test. The degree of mosaicism may vary over time in X-CGD carriers (Segal, Leto et al. 2000) as we shown in mother who began clinically with the recurrent and severe infections at 15 years old. Each carrier must be advice about that risk as a part of the genetic counseling.

In the 15 families in which we studied the grandmother we shown a carrier status in 8 and in 8 we did not evidenced it. It could be explained secondary to a *novo* mutation in *CYBB* gene

mother or an inactivation of the X-chromosome with the mutation providing a normal result in DHR assay. Molecular studies are the confirmatory tests.

X-linked carriers have a mosaic pattern of normal and defective neutrophils on oxidative testing by either DHR, ranging in most cases from 20% to 80% oxidase positive cells (Seger 2010). Carriers with 10% oxidase positive cells have normal host defense, in rare instances, as we found in the grandmother of the family 15.

In a cohort of 16 X-linked CGD carriers from Netherlands, 31% women had clinically discoid lupus. The fact that we found a minor percentage could be associated to ethnical factors, but could be explained secondary to a lack of diagnosis.

In conclusion we detected X linked inheritance pattern, as the most prevalent in a Mexican cohort of CGD male patients, the as has been reported in most of the countries around world.

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