Clinical Manifestations in Carriers of X-Linked Chronic Granulomatous Disease in Mexico

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Chronic granulomatous disease (CGD) is characterized by defects in NADPH oxidase, causing phagocytes to improperly clear invading pathogens. Owing to lyonization, X-linked CGD carriers (XL-CGD) have a dual phagocyte population, with 20% to 80% functioning phagocytes. Neutrophils with inactivation of the mutated X chromosome in the *CYBB* gene have a normal respiratory burst, whereas neutrophils with inactivation of the normal X chromosome have a CGD phenotype [1-3].

XL-CGD carriers exhibit a variety of autoimmune manifestations, mainly lupus-like signs and symptoms [3-5]. Skin diseases include recurrent photosensitive rash, folliculitis, postadolescent acne, eczema, and oral aphthous ulcers [1]. Gastrointestinal manifestations include abdominal pain, intermittent diarrhea, rectal bleeding, and chronic inflammatory bowel disease [6]. Recurrent infections characteristic of CGD include recurrent skin abscesses, pneumonia, hidradenitis suppurativa, and liver abscesses [2,5]. Other symptoms are chorioretinitis and fatigue [7]. All of these symptoms have an impact on quality of life.

No studies have documented the symptoms presented by XL-CGD carriers in Latin America. The aims of this study were to describe the main signs and symptoms of Mexican XL-CGD carriers and to correlate the percentage of neutrophils with normal production of hydrogen peroxide ($H_2O_2^+$) and various clinical variables.

Sixty-five XL-CGD carriers diagnosed from 2011 to 2018 were invited to participate, although not all accepted the invitation. Informed consent and/or assent were obtained from

all participants. Carriers were shown to have a dual phagocytic cell population, as confirmed by the 1,2,3-dihydrorodamine assay. A detailed health survey was administered to 42 female carriers from 29 kindreds to detect the presence of data suggestive of disease. The median age of the group was 39.2 years (range, 7-73 years). The relationship between the carriers and the CGD patients was as follows: 29 mothers, 9 grandmothers, 2 sisters, and 2 aunts. The mean (SD) percentage for $H_2O_2^+$ neutrophils was 47.9% (20.3%). The clinical manifestations are shown in the Table.

To determine whether a lower percentage of unaffected neutrophils ($H_2O_2^+$) was associated with the presence of the different clinical variables, a correlation was made between the different manifestations and 2 groups of carriers ($H_2O_2^+$ neutrophils ≤40% and $H_2O_2^+$ neutrophils >40%). The cut-off point was set arbitrarily according to the distribution of the sample.

Aphthous stomatitis and gingivitis were the only signs that were found to be statistically significant (Table). The remaining clinical variables were also analyzed; however, we did not find a statistically significant difference between the 2 groups.

The clinical manifestations reported in this cohort were all present, regardless of whether they had previously been associated with XL-CGD carriers [1-5]. As in other series, dermatological symptoms were reported in almost half of the participants. We also found a girl with ectodermal dysplasia, which had not been previously associated with having XL-

Table. Clinical Manifestations in 42 XL-CGD Carriers

Manifestation	No. (%) N=42	$H_2O_2^-$ ≤40% N=17	$H_2O_2^+$ >40% N=25	P Value[a]
Gastrointestinal manifestations				
Constipation	13 (31)	6 (35)	7 (28)	.616
Intermittent noninfectious diarrhea	9 (21)	2 (12)	7 (28)	.192
Gastroesophageal reflux	6 (14)	3 (18)	3 (12)	.466
Dermatologic manifestations				
Photosensitivity	17 (40)	7 (41)	10 (40)	.939
Postadolescence acne	10 (24)	5 (30)	5 (20)	.482
Recurrent cutaneous abscesses	3 (7)	1 (6)	2 (8)	.645
Ectodermal dysplasia	1 (2)	0 (0)	1 (4)	*
Rosacea	1 (2)	1 (6)	0 (0)	*
Autoimmune manifestations				
Arthralgia	18 (43)	5 (30)	13 (52)	.147
Aphthous stomatitis	15 (36)	11 (65)	4 (16)	.002
Fatigue	10 (24)	4 (24)	6 (24)	.627
Polyarthritis	7 (17)	1 (6)	6 (24)	.129
Autoimmune hemolytic anemia	1 (2)	0 (0)	1 (4)	*
Juvenile idiopathic arthritis	1 (2)	0 (0)	1 (4)	*
Sjögren syndrome	1 (2)	1 (6)	0 (0)	*
Discoid lupus	1 (2)	0 (0)	1 (4)	*
Rheumatoid arthritis	1 (2)	0 (0)	1 (4)	*
Infections				
Recurrent vaginal infections	12 (29)	7 (41)	5 (20)	.136
Recurrent lower urinary tract infections	12 (29)	7 (41)	5 (20)	.136
Recurrent rhinopharyngitis	8 (19)	4 (24)	4 (16)	.411
Pharyngotonsillitis	6 (14)	2 (12)	4 (16)	.534
Pneumonia	3 (7)	2 (12)	1 (4)	.355
Allergic rhinitis	2 (5)	2 (12)	0 (0)	.158
Liver abscess	1 (2)	1 (6)	0 (0)	*
Hidradenitis suppurativa	1 (2)	1 (6)	0 (0)	*
Other manifestations				
Miscarriage	14 (33)	4 (24)	10 (40)	.209
Gingivitis	14 (33)	9 (53)	5 (20)	.026
Chronic headache	13 (31)	4 (24)	9 (36)	.305
Transient blurred vision	8 (19)	6 (24)	2 (12)	.282
Insomnia	7 (17)	3 (18)	4 (16)	.603
Depression	5 (12)	3 (18)	2 (8)	.317
Hypothyroidism	3 (7)	3 (12)	0 (0)	.200

Abbreviations: XL-CGD, X-linked chronic granulomatous disease.
[a]Differences in percentages for categorical variables between the $H_2O_2^+$ ≤40% and $H_2O_2^+$ >40% groups were investigated using the Fisher exact test or χ^2 test where appropriate. Statistical significance was set at $P<.05$.
*No statistical analysis was performed because only 1 case was reported.

CGD in the literature; however, it is not possible to establish a correlation.

Battersby et al [6] reported on a cohort of 81 patients, of whom 40 (49%) had gastrointestinal symptoms, with the most frequent manifestations being abdominal pain and diarrhea. No definitive diagnosis was made in most cases; only 3 had a previous diagnosis of inflammatory bowel disease, and a further 3 were diagnosed during the study [6]. We found that the most frequent intestinal symptoms were chronic intermittent noninfectious diarrhea and constipation. However, endoscopic studies were not performed, and the diagnosis of inflammatory bowel disease was not confirmed.

We found 4 autoimmune diseases: rheumatoid arthritis, Sjögren syndrome, juvenile idiopathic arthritis, and hemolytic anemia. Previous studies have reported the frequency of discoid lupus to range between 8% and 40%, although we only found 1 carrier with discoid lupus among the total of the participating women, possibly because of ethnicity or environmental factors.

With regard to infections, the literature has reported a higher percentage of pneumonia and skin abscesses; however, in our study, genitourinary infections were the most frequent regardless of the percentage of $H_2O_2^+$ neutrophils. Marciano et al [2] found a strong association between the presence of severe infections and $H_2O_2^+$ neutrophils ≤20% [2], which we did not identify, possibly because of the reduced sample size. In our series, the only carrier with 5% $H_2O_2^+$ neutrophils presented with a liver abscess, recurrent genitourinary tract infections, and hidradenitis. Moreover, Rosen-Wolff et al [8] reported a 21-year-old carrier with 40% $H_2O_2^+$ neutrophils. These fell to 6%-8% 23 years later, and the patient developed pulmonary aspergillosis. Therefore, it is important to remember that the percentage of $H_2O_2^+$ neutrophils does not remain static in carriers, and the benefit of prophylaxis should be assessed in those with a low $H_2O_2^+$ neutrophil percentage.

Transient bilateral blurred vision was observed in a high percentage of patients in our cohort. Goldblatt et al [7] found a frequency of chorioretinitis of 10% in 30 female carriers. As this value could explain our findings, we recommend fundoscopy in the follow-up of XL-CGD carriers.

As for the obstetric features of XL-CGD carriers, Haidar et al [9] described the presence of recurrent chorioamnionitis in a carrier with 57% $H_2O_2^+$ neutrophils. We did not find this complication in our study population; however, 33% of the carriers had had a miscarriage not related to the percentage of $H_2O_2^+$ neutrophils. To our knowledge, this situation has not previously been reported in XL-CGD carriers. The considerably high percentage we observed should not be ignored in the comprehensive assessment of carriers.

In addition, XL-CGD carriers benefit from antibiotic and antifungal prophylaxis, along with regular monitoring, in much the same way as patients, although the evidence is still limited [10].

Finally, our findings suggest that XL-CGD carriers have a greater risk of autoimmune and/or infectious complications than was previously thought, many of which have received little recognition by medical professionals. Most would benefit from the specific medical attention of an immunologist or internist.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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