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High symptom burden in female X-linked chronic granulomatous disease carriers

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Highlights

- XL CGD female carriers are an underrecognized population.
- Autoimmune and inflammatory symptoms are the most commonly reported.
- An alarmingly high rate of psychiatric symptoms are reported in XL-CGD female carriers.

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Keywords

CGD; XL-CGD; Heterozygote

1. Introduction

Chronic granulomatous disease (CGD) is a rare inborn error of immunity caused by defects in the nicotinomide adenine dinucleotide phosphate (NADPH) oxidase complex which leads to impaired production of reactive oxidant superoxide anions within phagocytes [1]. Pathogenic variants in the genes *CYBB*, *CYBA*, *NCF1*, *NCF2,* and *NCF4*, which encode the structural components of the NADPH complex, or *CYBC1/EROS*, cause CGD. Measurement of decreased phagocyte superoxide anions is diagnostic of CGD. The measurement of phagocyte NADPH oxidase activation is often performed by flow cytometric detection of dihydrorhodamine 123 (DHR), a probe that fluoresces when reduced to rhodamine in the presence of superoxide. CGD is diagnosed by abnormal DHR indicating low or absent superoxide production and is characterized by susceptibility to invasive bacterial and fungal infections affecting the skin, lung, liver, bone, and lymph nodes [2]. Non-infectious, inflammatory and autoimmune symptoms due to a dysregulated inflammatory response are also hallmark of the disease [3]. Inflammatory bowel disease reminiscent of Crohn's disease affects nearly 50 % of patients with CGD [4]. Granuloma formation can be obstructive in the gastrointestinal and genitourinary tracts and can compromise normal function of the liver and lungs. Finally, patients with CGD are also at increased risk of autoimmune phenomena, either in isolation, such as autoimmune cytopenias, or as part of other conditionssuch as systemic lupus erythematosus, and rheumatoid arthritis [[5], [6], [7]].

The most common form of CGD is due to mutations in *CYBB* on the X-chromosome, accounting for approximately 65 % of cases [8]. Female carriers of *CYBB* pathogenic variants have two populations of neutrophils: one that express the paternal and another that expresses the maternal X chromosome. Through the process of lyonization or random X-inactivation, genes encoded on one X chromosome are silenced early in development [9]. Therefore, in female X-linked (XL) CGD carriers, there is one population of neutrophils with normal expression of *CYBB* and normal respiratory burst, and one with mutated *CYBB* with absent or greatly reduced respiratory burst [10]. With random X-inactivation, sufficient phagocytes expressing the non-mutated *CYBB* are usually present to protect XL-CGD female carriers from infection susceptibility. Rarely, however, unbalanced X-inactivation can lead to a low percentage of phagocytes with intact *CYBB* expression, resulting in low superoxide production [2]. Marciano and colleagues showed XL-CGD female carriers with <20 % normal superoxide producing neutropils are susceptible to infection with CGD-specific organisms increases. However, in the same study, degree of X-inactivation did not correlate with presence of autoimmunity indicating that lack of superoxide alone was not the only factor contributing to inflammatory disease and autoimmunity in CGD [7].

Autoimmune symptoms reported among XL-CGD female carriers have included discoid lupus erythematosus, Raynaud phenomenon, oral aphthous ulcers, and inflammatory bowel disease [[5], [6], [7], 11]. More recently Battersby et al [11] described negative impacts on quality of life among XL-CGD female carriers, indicating that their carrier state may be causing more substantial symptoms than previously recognized.

Management of CGD relies primarily on the prevention of infections with anti-microbial prophylaxis and interferon (IFN)-γ. Inflammatory and autoimmune symptoms often require treatment with immunosuppressive agents. Hematopoietic cell transplant (HCT) can be curative, resolving the infectious and inflammatory disease manifestations [12]. XL-CGD female carriers can also benefit from the same therapies that CGD patients receive, but there are no clear recommendations concerning which patients and at what time point these therapies should be initiated [5]. In cases of severely unbalanced lyonization, XL-CGD female carriers have also benefited from HCT [13].

To understand more broadly the clinical phenotype of XL-CGD female carriers, we sought to further characterize symptom burden, quality of life, and access to healthcare in a U.S. cohort of these individuals.

2. Methods

A 57-question survey was developed by the CGD Project Working Team within the Primary Immune Deficiency Treatment Consortium (PIDTC) and the CGD Association of America (CGDAA). The PIDTC consists of 47 centers in North America whose shared goal is to improve outcomes of patients with rare disorders of the immune system. It is part of the Rare Diseases Clinical Research Network. This anonymous, cross-sectional survey was, open to 300 CGDAA members who were reported XL-CGD female carriers, and was completed online between January–March 2021. The survey was administered in lay terms and was beta tested prior to opening for completion to the membership of the CGDAA.

Data were analyzed with descriptive statistics using Prism version 9, to present categorical responses as numbers and percentages of carriers who responded with a given social or health characteristic. Details regarding treatment were entered as free text responses and were therefore not analyzed.

3. Results

3.1. Population of survey respondents

The survey was completed by 171 female subjects with a mean age of 45 (range 15–85) years. Most (93 %) were family members of XL-CGD patients. Eighty-three percent of respondents were diagnosed as XL-CGD carriers by a combination of DHR (46.4 %), nitroblue tetrazolium (17 %), or familial genetic testing (39.2 %); 17 % were unsure how a diagnosis was established. Half held a bachelor's degree (25.3 %) or advanced degree (24.7 %) and two-thirds were employed either full time (50 %) or part time (16 %) (Supplementary Figs. 1A-D).

3.2. Overall health and performance status and follow-up with health care providers

Most reported good overall health (50 %) or fair health (32.4 %) (Supplementary Figs. 1G-H), but nearly half (48 %) reported health problems potentially related to being an XL-CGD carrier. Twenty-five percent of respondents reported that activities of daily living were impaired due to symptoms related or possibly related to being an XL-CGD carrier. Ten percent of all respondents had work hours restricted due to fatigue (26.7 %), depression and/or anxiety (13.3 %), or pain (13.3 %) (Supplementary Figs. 1E-G). Sixty-eight percent of respondents received care by a primary care physician, and 45 % by specialist(s) (Supplementary Fig. 1 H-I). When asked about barriers to accessing sub-specialty care, 18 % had not been referred to a specialist, and 12 % reported a lack of specialists in their communities.

3.3. Infections and prophylaxis

Ten percent of respondents reported treatment for an infection defined as unusual in healthy individuals [8] (Supplementary Figs. 2A-C). Thirteen respondents (13 %) reported history of infection with organisms commonly reported in CGD patients: *Aspergillus* spp. (*n* = 6), *Salmonella* spp. (*n* = 5), *Nocardia* (*n* = 1), and *Serratia marcescens* (n = 1). Twenty-seven percent of respondents were receiving anti-microbial prophylaxis, and 1 individual was receiving interferon-gamma prophylaxis.

3.4. Organ manifestations

Over half (61.4 %) of respondents reported symptoms in 4–7 organ systems, and 12.3 % reported symptoms in 8–10 organ systems. Fifty percent of respondents with symptoms reported in ≥4 organ were followed by specialist(s) and 73 % were followed by a primary care provider. Autoimmune and inflammatory diseases were commonly reported: dermatologic (87 %), gastrointestinal (79 %), musculoskeletal/neurologic (60 %), and rheumatologic/autoimmune (59 %) were most frequent (Fig. 1, Fig. 2). As previously reported, oral ulcers (68 %), photosensitive rashes (46 %) and discoid lupus (35 %) were the most common manifestations across all organ systems [[5], [6], [7]]. Among gastrointestinal manifestations, after oral ulcers (68 %), irritable bowel syndrome (29 %), chronic diarrhea (15 %), and inflammatory bowel disease (12 %) were most common. Treatment of gastrointestinal symptoms included steroids, salicylates, anti-diarrheal agents, laxatives, hydroxychloroquine, topical steroids, biologic modifiers, and surgery. Hepatobiliary disease was less common, but 5 % reported elevated transaminases and 5 % reported biliary disease. Rheumatic diseases included Raynaud's phenomena (20 %), systemic lupus erythematosus (8 %), and rheumatoid arthritis (7.4 %). Granulomas (2.2 %), and myositis, vasculitis, and scleroderma (1.5 % each) were reported in smaller numbers. Steroids, intraarticular joint injections, hydroxychloroquine, and etanercept were used to treat autoimmunity.

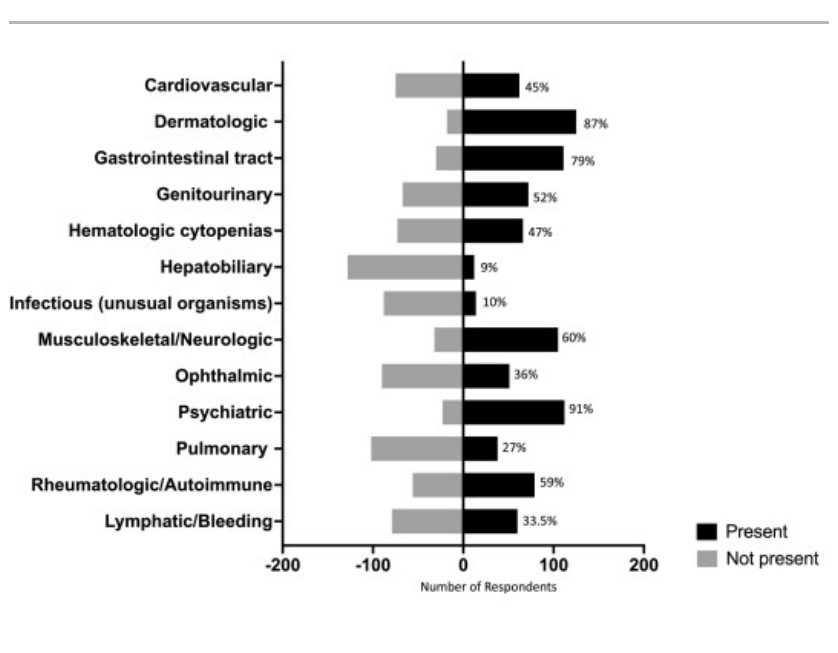

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Fig. 1. Overall Clinical Manifestations. Number of respondents with each organ system assessed in the survey. Percentages reflect the number of respondents who reported each organ manifestation over the total number of respondents for each category.

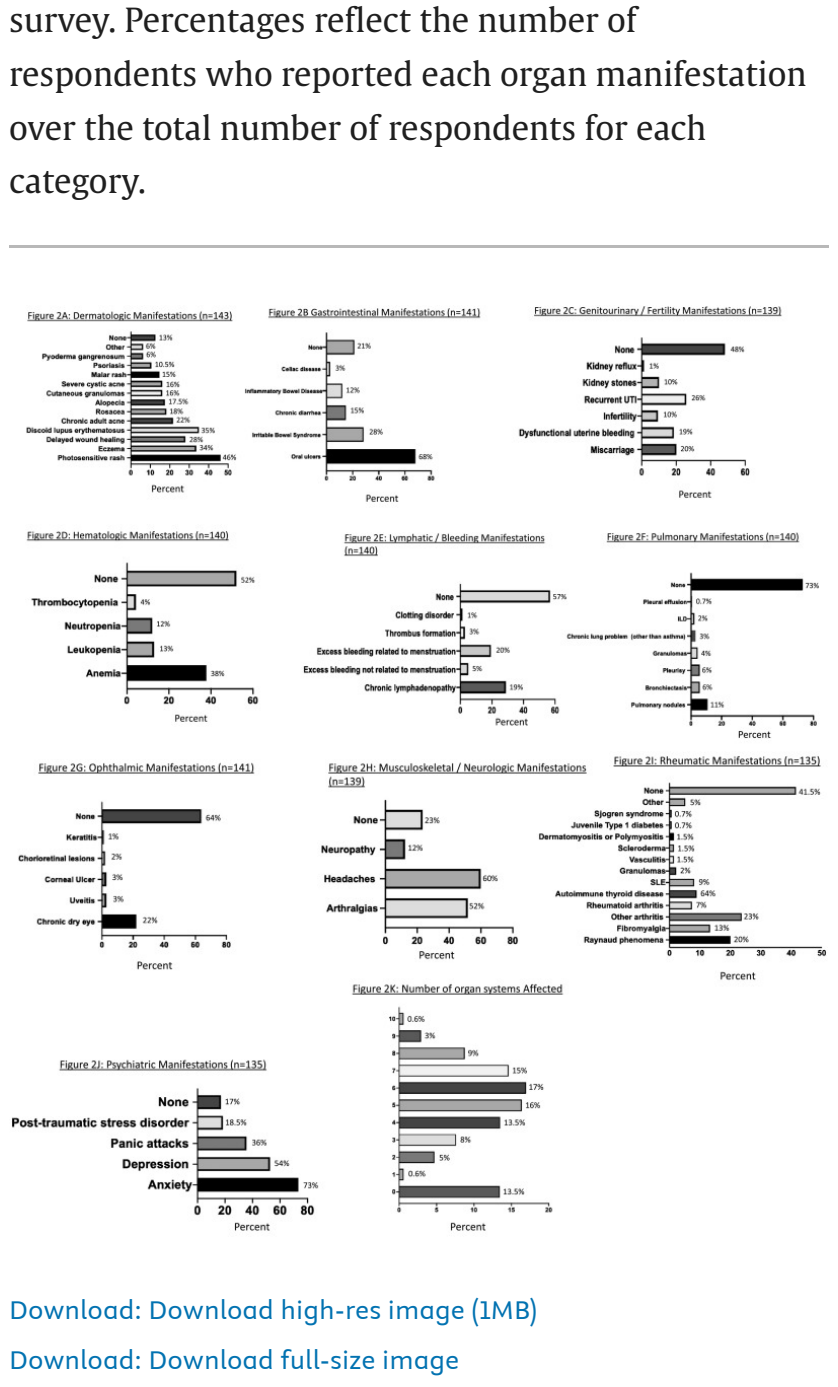

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Fig. 2. Self-reported Symptoms with Organ Systems Affected. A. Dermatologic Manifestations; B. Gastrointestinal Manifestations; C. Genitourinary / Fertility Manifestations; D. Hematologic Manifestations; E. Lymphatic / Bleeding Manifestations; F. Pulmonary Manifestations; G. Ophthalmic Manifestations; H. Musculoskeletal / Neurologic Manifestations; I. Rheumatic Manifestations; J. Psychiatric Manifestations; K. Number of Organ Systems Affected. For A-J, n = the number of respondents who completed responses for individual questions. Percentages reflect the number of respondents who reported each symptom over the total number of respondents for each category.

Cytopenias were reported by 48 % of carriers and were described as autoimmune in 24 % of these, not autoimmune in 12 %, and unknown cause in 64 %. Other hematologic manifestations included chronic lymphadenopathy, excess bleeding episodes, and hypercoagulability. Intravenous or oral iron, vitamin B12 injections, immunoglobulin infusions, steroids, splenectomy, laser ablation of the uterus, enoxaparin, phlebotomy, and hormone replacement were used to treat hematologic symptoms. Twenty-seven percent of respondents reported pulmonary disease which included pulmonary nodules, bronchiectasis, granulomas, and interstitial lung disease. Over half (64 %) with pulmonary symptoms received treatment including systemic or inhaled steroids, supplemental oxygen and/or surgery. Recurrent urinary tract infections (26 % of respondents) and dysfunctional uterine bleeding (19 %) were the most frequent genitourinary complaints. A small subset of respondents reported miscarriage(s) (20.4 %) and/or fertility problems (9.4 %). Malignancy was reported in 4.7 %.

Self-reported psychiatric symptoms were noted by 91 % of respondents and included: anxiety (73 %), depression (53 %), panic attacks (36 %), and post-traumatic stress disorder (17 %). Nearly half (46 %) were receiving counseling, and/or medication.

4. Discussion

In this largest analysis of XL-CGD female carriers reported to date, frequent self-reported symptoms affecting nearly every organ system are apparent. Our cohort of XL-CGD female carriers reported a high degree of susceptibility to autoimmune and inflammatory diseases, similar to patients affected with CGD who are susceptible to systemic autoimmunity and autoinflammation that can be difficult to treat [14]. Also similar to patients with CGD, treatment relied heavily on use of corticosteroids and other immunosuppressive agents. A small subset of XL-CGD carriers were susceptible to CGD-related infections (17.5 %) and over one quarter (27.3 %) of respondents were receiving antimicrobial prophylaxis.

A striking finding within this cohort was the high prevalence of mental health symptoms. Battersby et al [11] reported anxiety, depression, and low self-esteem in a cohort of 62 female carriers of XL-CGD. In our cohort, 91 % reported mental health symptoms, however, over half (54 %) were not currently receiving treatment for these symptoms. The cause of mental health symptoms is unclear although rates of depression and anxiety are known to be higher in caregiver populations [15], and most respondents were mothers of sons with XL-CGD.

Despite the frequency of symptoms reported, nearly half of respondents reported good overall health. However, only half of respondents reported full time employment and a quarter had work-related restrictions due to health-related symptoms. One of the most common symptoms reported in patients with chronic disease was fatigue [16]. Among XL-CGD female carriers, fatigue was the most commonly reported symptom limiting daily activities and leading to work restrictions.

Carriers of XL-CGD have traditionally been thought to be unaffected or minimally affected; however, this survey indicates that these females have a variety of symptoms and disease manifestations that may warrant monitoring. Our data show that fewer than half of respondents had been or were under care of specialists, including those with the highest reported symptom burden and 32 % were not followed by a primary care provider. Rheumatologists and immunologists were the most common specialists providing clinical care to carriers, but other specialties were also consulted. There are several reasons that a lack of specialist care was observed, including: lack of specialist care in an individual geographic area, poor understanding of the possible link between the symptom and the XL-CGD carrier diagnosis, or reported symptoms were able to be managed without specialty care based on the assessment of the primary care provider. The authors recommend that all XL-CGD female carriers be followed by primary care providers, and at a minimum, every clinical visit include a review of systems (example in Supplemental Table 1) with additional evaluation by appropriate specialists as needed.

Limitations of this study include an inability to make causal statements, since symptoms were self-reported, and lack of details regarding medical management of symptoms. Because symptoms were self-reported, they could be over and/or under reported, including under reporting of multi-organ symptoms, especially in those not routinely followed by appropriate specialists. Further, the results may have been biased by only XL-CGD female carriers with symptoms since the survey was open to all irrespective of clinical history. Lastly, due to the lack of a non-carrier comparison population, we were unable to correlate subject superoxide production with symptoms. Nonetheless, the unusually high incidence of significant morbidities in this cohort of XL-CGD female carriers indicates a need for regular medical and mental health evaluation, to include specialist evaluations as needed. Future studies in this population are warranted.

Clinical implications

XL- CGD female carriers suffer from a variety of medical problems, many of which overlap with symptoms of CGD. Female carriers require close monitoring by appropriate medical specialists.

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