

Abstracts from ESID

THE HEALTH OF CARRIERS OF X-LINKED CHRONIC GRANULOMATOUS DISEASE IN THE UNITED KINGDOM

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Background

X-linked (XL) CGD, a rare primary immunodeficiency due to *CYBB* mutations leading to defective gp91^{PHOX}, results in decreased/absent respiratory oxidative burst. High rates of discoid lupus have been reported in XL-carriers. Current literature about XL-CGD carrier health is limited to small series and anecdotal reports. We undertook a large in-depth study of XL-CGD carriers.

Methods

XL-CGD families were identified and XL-carriers recruited. Participants completed detailed questionnaires about their medical health with particular attention to SLE and gastrointestinal (GI) symptoms. Affected and unaffected groups were compared by t-tests to see if age/neutrophil oxidative burst (NOB) were significant.

Results

71 recruited (study remains open). Mean age 43 years (3-77).

Mean NOB 50% (9-94%)

Photosensitivity, mouth ulcers and joint symptoms occurred in >60%.

GI symptoms present in >50%. 10 had undergone invasive investigations. 4 diagnosed with Inflammatory Bowel Disease (IBD).

	Affected	Unaffected
Recurrent Ulcers	54	17
Raynaud's	25	46
Joint Pain	45	26
Photosensitivity	52	19
GI Symptoms	37	34
Recurrent Skin Abscess	6	65

Age was not significantly different in affected/unaffected groups.

NOB value was significant ($p=0.02$) only for recurrent skin abscess (lower value more associated with abscesses).

Discussion

The study's strength is the detail collected. It is the largest, most comprehensive study of XL-CGD carriers to date.

The main finding is significant medical problems are more common and diverse than previously considered. The overlap with IBD has not been previously described, highlighting the association between CGD colitis and IBD.

XL-CGD carriers are at greater risk of medical problems than previously thought. Symptoms do not correlate well with NOB or age. Greater awareness of potential medical problems is required.

The Psychological Health of X-linked Carriers of Chronic Granulomatous Disease in the United Kingdom

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Background

CGD is a rare primary immunodeficiency consisting of recurrent infection and inflammation. 70% of UK cases are X-linked (XL). Female carriers are usually confirmed after a relative's diagnosis. XL carriers have several risk factors for psychological health problems; a family member with chronic illness, their own medical problems and an association with SLE. SLE is associated with anxiety and depression.

Methods

XL CGD carriers, identified as relatives of an index case from the CGD Registry, were recruited. Participants completed validated psychological health questionnaires; Hospital Anxiety and Depression Score (HADS) and Pediatric Inventory for Parents (PIP).

Data were compared to published norms and published data from comparable groups. A HADS score above 7 (anxiety/depression) is abnormal[1]. Symptom frequency was compared with parents of CF children [2]. HAD mean scores were compared with SLE patients published data [3].

PIP scores distress due to parenting a chronically unwell child with sub-scores about frequency (PIP-F) and severity (PIP-S). PIP's validation in oncology patients provides comparison data [4].

Results

HADS

54 completed

No significant difference between CGD carrier mothers and other relatives.

66% XL-CGD carriers greater than borderline anxiety, significantly more frequent than CF parents.

	CGD Carriers	SLE (High-Pain)	SLE (Low-Pain)
Anxiety	9.6	9	4
Depression	5.0	8	3

PIP

45 Mothers completed.

CGD scores similar to oncology parents, but higher PIP-F scores (p 0.006).

No correlation between PIP and anxiety/depression symptoms ($r < 0.3$)

Discussion

CGD carriers had significant rates of anxiety, greater than that seen in CF parents. Lack of correlation between HADS and PIP suggests the cause for anxiety was not solely related to their child's disease.

This study highlights that XL CGD carriers suffer unrecognised but potentially significant psychological health problems which may impact upon their own lives and their ability to cope with the medical needs of their affected children.

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2. Besier, T., et al., *Anxiety, Depression, and Life Satisfaction in Parents Caring for Children With Cystic Fibrosis*. Pediatric Pulmonology, 2011. **46**(7): p. 672-682.
3. Waldheim, E., et al., *Health-related quality of life, fatigue and mood in patients with SLE and high levels of pain compared to controls and patients with low levels of pain*. Lupus, 2013. **22**(11): p. 1118-1127.
4. Streisand, R., Braniceki, S, Tercyak, KP, Kazak, AE, *Childhood Illness-Related Parenting Stress: The Pediatric Inventory for Parents*. Journal of Pediatric Psychology, 2001. **26**(3): p. 155-162.

QUALITY OF LIFE (QOL) IS REDUCED IN X-LINKED CARRIERS OF CHRONIC GRANULOMATOUS DISEASE (CGD)

Background

X-linked (XL) CGD is a rare primary immunodeficiency due to mutations in *CYBB* leading to defective gp91^{PHOX} (an NADPH oxidase complex subunit) resulting in decreased or absent respiratory oxidative burst. XL-carriers have a high

incidence of discoid lupus. Other symptoms are anecdotally reported. Carrier status is usually confirmed after a relative has been diagnosed with CGD.

Methods

XL-CGD families were identified and carriers recruited. Participants completed a validated QoL questionnaire; the SF36v2. Means for each domain were compared with published UK norms using a one-sample t-test.

Results

49/78 XL-carriers (34 mothers) completed the SF36v2.

QoL was reduced in all domains.

Domain	CGD Carriers	UK Norms (female age 35-54)[1]	P-value
Physical Function	79.28 (29.4)	89.4(18.3)	0.0099
Role Physical	74.35(32.2)	84.0(32.0)	0.00235
Bodily Pain	66.24(30.5)	79.4(22.0)	0.002
General Health	56.31(28.5)	74.1(20.3)	0.00
Vitality	44.98(25.5)	58.2(19.9)	0.002
Social Function	69.68(29.5)	86.7 (20.5)	0.001
Role Emotional	71.88(31.3)	80.3 (33.6)	0.0341
Mental Health	63.16(16.8)	71.6(17.8)	0.005

Table 1: SF36 Mean Scores for CGD XL-Carriers and UK Norms

Discussion

This study demonstrates that QoL is reduced in XL-CGD carriers compared to population norms.

There may be several reasons for this. We have demonstrated elsewhere that XL-CGD carriers have more medical problems than previously described. The majority of participants in this study (70%) were mothers of CGD children: the stresses associated with caring for a child with CGD may adversely affect QoL.

The importance of this study is that XL-CGD carriers have not previously been shown to have significant problems yet these findings demonstrate that QoL is significantly reduced when compared with similarly aged women.

High Fatigue Levels in XL-CGD Carriers associated with raised serum IL-8

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Background

Chronic Granulomatous Disease (CGD) is a rare primary immunodeficiency, of which 70% of cases are X-linked (XL). We have recently found that XL-CGD suffer from inflammatory complications of CGD (ESID Poster).

Methods

During a study of health of XL-CGD carriers we investigated symptoms of excessive fatigue using the Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF). Serum levels of pro-inflammatory cytokines (IL-1 α , IL-5, IL-8, IL-10, IL-17, TGF β 1, IFN α and IFN- γ) were measured on stored serum from 52/81 subjects, collected during the original research study, by Cytometric Bead Array (CBA) immunoassay using a BD Biosciences LSRFortessa™ cell analyser. Results were compared with inflammatory disease control groups of 10 high and 10 low fatigue Sjogren's disease patients and 15 healthy controls. XL-CGD carriers were divided into two groups; those who reported fatigue and those that did not.

Results

50% of XL-CGD carriers reported suffering excessive fatigue, associated with significantly higher scores in the MFSI-SF ($p < 0.01$) XL-CGD carriers have significantly higher serum IL-8 levels than normal controls ($p =$), but similar levels to patients with Sjögrens disease.

XL-CGD carriers reporting high levels of fatigue have significantly higher IL-8 levels, than those not reporting fatigue ($p = 0.017$). No other cytokines reached statistically significant different levels, between groups.

Discussion

XL-CGD carriers report higher fatigue levels than expected, and there is association between fatigue and raised IL8 in carriers, and in patients with Sjorgren disease, suggesting a biological explanation for the symptoms. IL1 β levels were not significantly raised. Previous studies have associated pro-inflammatory states with excessive fatigue. Further research is required to evaluate this finding in XL-CGD carriers.