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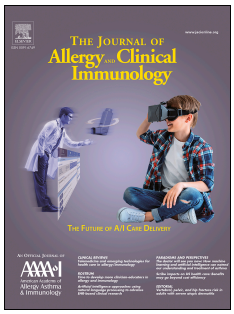

LONG-TERM OUTCOMES FOR ADULTS WITH CHRONIC GRANULOMATOUS DISEASE IN THE UNITED KINGDOM

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Capsule Summary: Uncorrected CGD is associated with significant morbidity and mortality in adulthood, in particular due to inflammatory complications including life-limiting interstitial lung disease.

Key words:

Chronic Granulomatous Disease

adult

outcome

morbidity

survival

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68 **Abbreviations:**

CGD	Chronic Granulomatous Disease
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
CYBB.	Gene coding for Cytochrome b(-245), β subunit ($gp91^{Phox}$)
$gp91^{Phox}$	91- kDa glycosylated β chain; Cytochrome b(-245), β subunit
NCF1	Gene coding for Neutrophil Cytosolic Factor 1 ($p47^{Phox}$)
NCF2	Gene coding for Neutrophil Cytosolic Factor 2 ($p67^{Phox}$)
CYBA	Gene coding for Cytochrome b(-245), α subunit ($p22^{Phox}$)
NCF4	Gene coding for Neutrophil Cytosolic Factor 4 ($p40^{Phox}$)
CYBC1	Gene coding for Cytochrome b(-254) chaperone 1 (EROS)
$p47^{Phox}$	Neutrophil Cytosolic Factor 1
$p67^{Phox}$	Neutrophil Cytosolic Factor 2
$p22^{Phox}$	22 - kDa non glycosylated α chain; Cytochrome b(-245), α subunit
$p40^{Phox}$	Neutrophil Cytosolic Factor 4
EROS	Cytochrome b(-254) chaperone 1
UK	United Kingdom
HSCT	Hematopoietic Stem Cell Transplantation
NHS	National Health System
NBT	Nitroblue Tetrazolium Test
DHR	Dihydrorhodamine 123
CT	Computerized Tomography
GI	Gastrointestinal
COPD	Chronic Obstructive Pulmonary Disease
HPV	Human Papilloma Virus
HIV	Human Immunodeficiency Virus
DLCO	Diffusing capacity of the lungs for carbon monoxide
XL	X linked
AR	Autosomal Recessive
HRCT	High Resolution Computerized Tomography
IBD	inflammatory bowel disease
MRI	Magnetic resonance imaging

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To the Editor:

Chronic granulomatous disease (CGD) is an inherited primary immunodeficiency caused by genetic defects that impact the structural subunits or function of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. Consequent reduction in respiratory burst impairs phagocyte function causing granulomatous inflammation and recurrent life-threatening bacterial and fungal infections (1–3). Although clinically variable with respect to presentation and disease severity (1,4), improvement in life expectancy now allows most patients to reach adulthood even without corrective therapy. However, the clinical course of CGD for those who reach adulthood remains poorly documented. In the few large multicenter studies published, data for adults has mainly been combined with pediatric data (1–6) and the only targeted study of adult CGD outcomes reported high levels of morbidity and early mortality (7). As improved survival following corrective hematopoietic stem cell transplantation (HSCT) has expanded this option for treating both asymptomatic children and symptomatic adults with CGD, accurate data for outcomes and quality of life for conservatively managed CGD in adulthood are urgently required to improve counselling for patients and families considering curative treatment. Our objective in this study was to evaluate the long-term clinical course of uncorrected CGD adult patients in the United Kingdom.

Fifty-three patients met the inclusion criteria for our study (details of study methodology can be found in Supplemental Material and Methods), 44 of whom were cared for at a single centre which runs a dedicated CGD clinic. All patients were prescribed continuous antibacterial and antifungal medication, typically

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cotrimoxazole and itraconazole, for infection prophylaxis. No patients received interferon gamma as prophylaxis. The features of the cohort are summarized in Table 1. Data were collected for a total of 891 years of observation, with a mean of 17 years per patient (range 0.45 -54 years).

A total of 178 infectious events were recorded during 891 years of follow-up, giving an annual incidence of 0.2 infections per patient. The causative pathogen was isolated in only a minority of cases (16%) with *Staphylococcus aureus* and *Aspergillus sp.* most commonly found, as previously described (8). Additional details for sites of infection and pathogen can be found in Tables E1 and E2 in this article's online repository.

A total of 117 hospitalizations in 37/53 patients were seen over the observation period. Pneumonia and exacerbation of chronic pulmonary disease were the major reasons, followed by gastrointestinal complications and major gastrointestinal surgeries (for further details see Table E3 in this article's online repository). 70% of patients had at least one hospital admission during the follow up period (Figure E1 in this article's online repository), with no correlation between the number of hospital admissions and duration of follow up or genetic type of CGD (P-value > 0.05). Compliance with treatment was not well documented and therefore could not be assessed as a variable that could influence repeated hospital admissions. A total of 23 patients (43%) had active GI disease in adulthood. Of these, the onset of GI symptoms was documented in childhood for 11/23 (48%) and in adulthood for 8/23 (35%) (Table E4 in this article's online repository). Steroids and aminosalicylates were the main medical treatments recorded in adulthood (used in 8 and 11 patients respectively) with biological agents such as infliximab and

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adalimumab used in a minority (3 patients recorded). 11/23 (48%) patients with active GI disease in adulthood underwent surgical intervention, which we classified as major (colectomy, ileostomy, colostomy or proctectomy) or minor (fistula repair or perianal abscess drainage). Of those who required intervention at any time in life, 5/11 (45%) had both major and minor surgeries while 3/11 (27%) had major surgery only and 3/11 (27%) patients required minor surgery only. The majority of surgical interventions happened in adulthood (21 vs 4 events) but there was no difference in the percentage of patients requiring surgery when pediatric and adult onset GI disease was compared.

Of importance, 3 episodes of bowel cancer were seen including squamous cell anal carcinoma in a patient age 30 years with X-CGD and perianal fistulas, one HPV associated anal intraepithelial neoplasia in a patient age 37 with X-CGD, HIV coinfection and colitis and one colon adenocarcinoma in a female patient age 66 years who also had colitis since age 35. Separately, testis teratoma was seen in one patient at the age of 25 years and pancreatic cancer in a 36 year old female patient.

Pulmonary complications were common in our cohort. Of the 29 patients with CT scan reports available, 28 (96%) had an abnormality reported. 22 high resolution CT chest scans of 22 patients were reviewed by a specialist radiologist at our centre and scored according to specified criteria. Of these, 15 scans were documented to be performed for routine monitoring purposes and 5 for investigation of acute symptoms (fever, cough or weight loss).

Twenty-one out of 22 (95%) chest CT scans were abnormal (see Table E5 in this article's online repository). The most frequent features were nodules (20 patients;

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90 %), scarring (19 patients; 86%), bronchiectasis (14 patients; 64%) and ground glass change (10 patients; 45%). Emphysema (9 patients; 40%), air trapping (7 patients; 32%), pleural thickening (2 patients; 9%) and enlarged lymph nodes (1 patient; 4.5%) were also seen in our patients. Out of the 9 patients with emphysema with a mean age of 35 years, 4 had no prior history of smoking.

A total of 29 patients had respiratory function tests; abnormalities were found in 20 (69%) of these. Obstruction was more frequently seen than restriction (9 vs 6 patients; 45% vs 30 %). However, the most frequently observed abnormality was low diffusion capacity, found in 15 out of 24 patients tested (62%) and which occurred in 5 patients despite normal spirometry. Further analysis of correlation of CT changes and lung function is presented in Table E5 in this article's online repository. Importantly, X rays were often normal (11/23; 48%) even in patients with significant changes on CT chest and/or impaired lung function tests, indicating that this modality is not sufficiently sensitive for diagnosis in CGD.

Five deaths (9.4%) occurred during the follow-up period, at a mean age of 50.7 years and a median of 47.8 years (range 36-71). Causes of death were respiratory failure secondary to chronic lung disease in four cases; 3 in AR CGD and 1 in X-CGD at ages 44, 71,38 and 50 years respectively. Pancreatic cancer resulted in 1 death in patient with AR CGD at age 36 years. While survival at median age of follow up (30 years) was 100%, the survival probability for all patients was 94.7%, 88%, 79% and 59% at ages 36, 38, 44 and 50 respectively (Figure 1). In this cohort, patients with residual respiratory burst were not less likely to die or require major medical intervention (hospital admission for infection, major GI

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surgery or HSCT when compared to patients with absent oxidative burst (see Table E.6 in this article's online repository).

This is the first study carried out in the UK aiming to evaluate the long-term clinical course of uncorrected CGD in an adult population, largely looked after at a single center that holds a national CGD service. Non-infectious gastrointestinal and pulmonary complications were the major causes of serious morbidity in this study.

Active chronic inflammatory gut disease in adulthood was more prevalent than in previous studies (3,4,7), frequently requiring surgical intervention and in some cases associated with gastrointestinal malignancy, which suggests that patients with GI manifestations would benefit from colonoscopy and MRI scans screening.

Onset in adulthood did not predict less severe disease. Chronic pulmonary complications, highlighted by other studies (5–9), were almost unanimous in our cohort with a high prevalence of presumed non-infectious inflammatory changes on high resolution CT, including early onset of emphysema seen even in the absence of smoking. Low diffusion capacity was seen both with and without CT changes and despite normal spirometry, suggesting that this might be an early indicator of inflammatory lung disease and a useful tool to monitor these patients. Of importance, the 9.4% overall mortality rate observed in our conservatively managed CGD cohort was predominantly related to chronic respiratory failure.

Overall, our data indicate that adults with CGD live with significant and progressive morbidity, predominantly related to inflammatory complications. With rapidly improving outcomes for HSCT in CGD and progress with gene

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therapy approaches, the long term complications associated with uncorrected CGD are an important consideration when counselling patients and families for stem cell treatments.

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TABLE I. General Characteristics of the Study population

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Age at onset of symptoms (y), mean (range)	6.2 (0-29)
Age at end of follow up (y), mean (range)	33 (16-70)
Male, n (%)	41 (77)
Female, n (%)	12 (23)
Inheritance and genotype, n (%)	
X-linked	33 (62)
CYBB, gp91Phox	30 (56.6)
No genotype or protein available	3 (5.6)
Autosomal Recessive	20 (38)
NCF1, $p47^{Phox}$	13 (24.5)
NCF2, $p67^{Phox}$	2 (3.8)
CYBA, $p22^{Phox}$	1 (2)
No genotype or protein available	4 (7.5)
Mode of presentation, n (%)	
Skin infection	15 (28)
Liver Abscess	9 (17)
Pulmonary Infection	8 (15)
Family screening due to index case	6 (11)
Salmonella gastroenteritis *	4 (8)
Colitis	3 (6)
Lymphadenitis	3 (6)
Granulomatous Obstruction	1 (2)
Osteomyelitis	1 (2)
Unknown	9 (17)
Deaths, n of patients (%)	5 (9.4)
Mean age (y), range	50.7 (38-71)
Causes of death, n	
Respiratory failure	4
Pancreatic cancer	1

* 1 patient also had *Salmonella* sepsis

All patients were prescribed continuous antibacterial and antifungal medication, typically cotrimoxazole and itraconazole, for infection prophylaxis. IFNγ was not used.

1 male patient had well controlled HIV coinfection acquired in adulthood.

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Figure 1: Kaplan-Meier overall survival curve after transition to adult services for the entire cohort of patients. The number of patients alive at specific time points are shown below.

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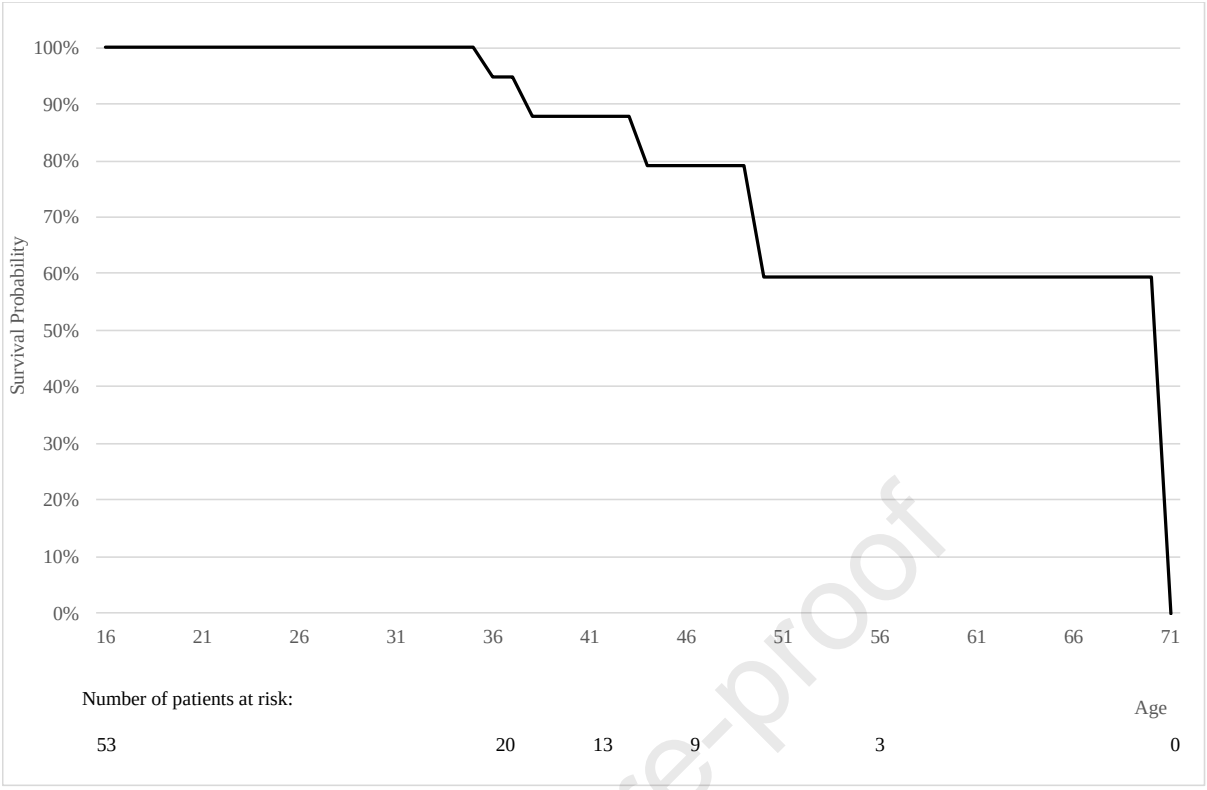

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