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Special Article: Chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry

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Summary

There are no epidemiological studies from the British Isles of chronic granulomatous disease, characterized by recurrent, life-threatening bacterial and fungal infections and inflammatory sequelae. Patients were enrolled in a national registry and medical records were analysed. Of 94 subjects, 69 had X-linked disease, 16 had autosomal recessive disease and nine were unknown. Prevalence was 7·5/million for 1990–99 and 8·5/million for 1980–89. Suppurative adenitis, abscesses and pneumonia presented commonly. Twenty-three of 30 patients who underwent high resolution computerized tomography had chronic respiratory disease. Inflammatory sequelae included bowel stricture and urogenital tract granulomata. Growth failure was common; 75% of those measured were below the population mean. All patients received prophylactic antibiotics and 93% anti-fungal prophylaxis. Interferon gamma was used to treat infection, but rarely as prophylaxis. Despite prophylaxis, estimated survival was 88% at 10 years but 55% at age 30 years. Morbidity remains significant, severe infectious complications common. Curative treatments including stem cell transplantation should be considered for patients with frequent or serious complications.

Keywords: Aspergillus infection, chronic granulomatous disease, colitis, pneumonia, Staphylococcal infection

Introduction

Chronic granulomatous disease (CGD) is a rare inherited primary immunodeficiency, first described in the 1950s, in which defective phagocyte killing renders patients susceptible to severe, recurrent life-threatening bacterial and fungal infections [1,2]. Inheritance is usually X-linked (XL), but can be autosomal recessive (AR). Defects in components of nicotinamide adenine dinucleotide phosphate-oxidase leave phagocytes unable to generate reactive oxygen radicles necessary to eliminate ingested organisms [3–8]. Patients are particularly susceptible to fungal infection, typically from *Aspergillus* species, but also catalase positive bacteria including *Staphylococcus aureus* and *Burkholderia cepacia*. Most patients present with infections, typically lymph node abscesses, but also recurrent respiratory infection, deep-seated abscesses and septicaemia [7,9–11]. Inflammatory sequelae are recognized increasingly, notably colitis, which resembles Crohn's disease [12–14]. Since the 1960s, improved tests mean that CGD can be diagnosed easily and accurately [15,16]. More recently, the use of prophylactic antibiotics and anti-fungal agents appears to have reduced morbidity and mortality in cohorts of patients seen in specialist clinics, but CGD remains a life-threatening condition [17–19]. However, little is known of the clinical course, complications and risk of death in UK and Irish CGD patients, as there are no epidemiological studies. In 2000, the United Kingdom and Ireland CGD Registry was established to ascertain the epidemiology, clinical features and outcomes for patients with different forms of CGD at all ages. We report the findings.

Methods

Participants

Patients with a confirmed diagnosis of CGD, resident in the United Kingdom and Ireland at the time of diagnosis, alive at onset of the study (September 2000) or diagnosed between then and 31 December 2001, were included. A diagnosis of CGD was accepted if there was a clinical history consistent with CGD, and at least one confirmatory laboratory result. Diagnostic tests used included nitroblue tetrazoluene (in 82 patients), dihydrorhodamine fluorescence (17) and chemiluminescence (39) tests.

Inheritance was considered XL if a boy's mother or sister had a dual population of normal and abnormal neutrophils, if a male relative of the mother had CGD or if the patient had abnormal gp91 on Western blot analysis. AR inheritance was considered if there were affected brothers and sisters in the same family and if the patients' mothers' oxidative burst was normal. The result of genetic mutation analysis was available for some patients.

Case ascertainment

Multi-regional Ethical Committee approval was obtained. Physicians throughout the United Kingdom and Ireland in subspecialities caring for CGD patients, identified through hospital directories and specialist organizations, were invited to enrol patients. A total of 1684 consultants were contacted: those reporting CGD patients were sent information packs and consent forms for their patients, who were asked to return completed consent forms to the study team. Registry details were placed on the Chronic Granulomatous Disorder Research Trust website (http://www.cgd.org.uk) and newsletter. Patients contacting the study team directly were sent information packs and consent forms. Initial non-responders were followed-up by reminder letters.

Data collection

Detailed data abstraction forms were used to collect comprehensive epidemiological and clinical information, including presenting and diagnostic symptoms, details of organ-specific problems, results of investigations and treatments prescribed. One of three researchers visited patients' hospitals and abstracted information directly from medical records. Population statistics for the United Kingdom were obtained from the Office of National Statistics, and for Ireland from the Central Office of Statistics, Ireland. Prevalence rates were calculated and presented with 95% confidence intervals (CI). Adjusted birth prevalence was calculated as described in the supplementary data. All analyses were performed using 95% CI calculated by STATA 8© (StataCorp LP, TX, USA).

Mortality

As the registry was a cross-sectional study, mortality and survival were estimated by comparing the number of patients on the registry in a given age group, with the number expected from the birth prevalence of CGD (7·5 per million). To assess mortality, physicians were asked to notify the study team of patients under their care who had died, and death certificates citing CGD were sought through the Office of National Statistics for all patients up to the age of 45 years. Patients up to age 45 years were included as this represented two time-periods in the International Classification of Disease codes, and there were few data on patients surviving longer than their 5th decade. Kaplan–Meier survival plots were calculated for the entire CGD population, as well as by gender and mode of inheritance.

Table 1. Ages at diagnosis and by gender.

Mode of inheritance	No. of patients	Median age (years)	Range (years)
All	94	2·7 years	0–51·1
Females	7	15·3	0·9–32·8
Males	87	2·5	0–51·1
XL	69	2·1	0–23·6
AR	9	17·8	1–51·1
Unknown	9	4·1	0·9–11·5

XL, X-linked; AR, autosomal recessive.

Results

A total of 1483 consultants replied (83%), identifying 145 patients, 119 of whom fulfilled the inclusion criteria. Twelve patients who were resident abroad, 12 who had died prior to the study commencing and two in whom the diagnosis was not confirmed were excluded; 94 patients consented to the study. One refused consent and consultants asked the study team not to contact seven patients. Detailed data were abstracted from 118 records at 26 different hospitals, covering 1411 follow-up years: 821 years for patients with XL disease, 439 years for those with AR disease and 151 years for patients for whom the mode of inheritance was unknown. Information was abstracted at more than one hospital for 24 patients.

Forty-five (48%) patients had more than one diagnostic test. Eighty-seven (93%) patients were male. The mode of inheritance was known in 85 cases; 69 (81%) had XL disease and 16 (19%) AR disease. The subtypes of AR disease were known in seven patients and exact mutations in 29 of the XL patients. Mode of inheritance was undetermined in nine (10%) cases (Table 1). The patients came from 77 nuclear families; 40 patients had at least one first- or second-degree relative with CGD. There were 80 reported carriers.

The median age at diagnosis was 2·7 years, being significantly lower for men and those with XL disease ($P < 0·005$). Although 37 (39%) patients were diagnosed before age 2 years and a further 25 (27%) before age 5 years, 10 (11%) patients were not diagnosed until their second decade and two (6%) were in their third decade or older. The birth prevalence of CGD was first estimated using cases born between 1994 and 1997 to limit possible bias caused by deaths of patients born in earlier years, and because some cases born in subsequent years would not yet have been diagnosed. During this period there were 3079 000 births in the United Kingdom and Ireland, of whom 23 had CGD, giving a birth prevalence of 7·47 per million (95% CI 4·63–10·99 per million). Between 1980 and 1989 the birth prevalence was 8·5 per million, and between 1990 and 1999 was 7·5 per million.

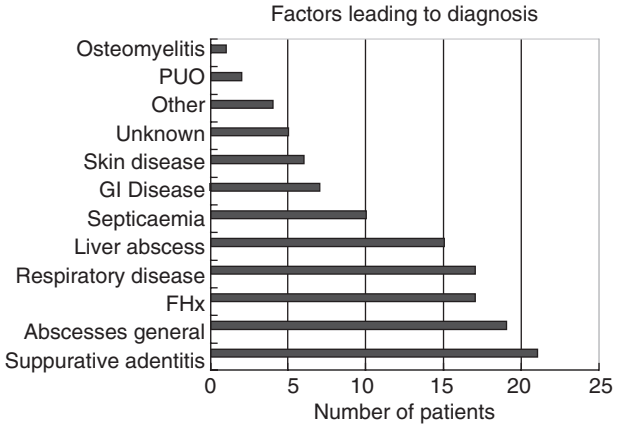


Fig. 1. Factors leading to the diagnosis. PUO, pyrexia of unknown origin; GI, gastrointestinal; FHx, family history.

Secondly, adjusted birth prevalence was calculated to allow for the different ages at diagnosis, giving prevalence rates of 11·4 and 14·6 per million for the decades 1980–89 and 1990–99 respectively. For the decade 1990–99 the adjusted birth prevalence for men was 15·9 per million and for women was 9·7 per million.

Clinical findings

Suppurative adenitis, abscesses and pneumonia were the most common presentations (Fig. 1). Seventeen patients were diagnosed because of a positive family history, 12 before becoming symptomatic. The number of infections, age of occurrence and organisms isolated are shown in Tables 2 and 3. There were 38 proven fungal infections in 25 (27%) patients at a median age of 14·2 years (range 1·2–54·5 years).

Pneumonia was the most common infection; radiological abnormalities were documented in 88 (84%) of 105 episodes. Bronchoalveolar lavage was performed in 22 (45%) patients; a further nine (18%) underwent lung biopsy. Seven patients required hospitalization for pneumonia before age 1 year, and 13 before 5 years. Twenty-three patients had recurrent episodes (range 2–9). *S. aureus* and *Burkholderia* species, respiratory pathogens reported in other series, accounted for only nine cases where organisms were identified. *Aspergillus* species were isolated in 13 cases and suspected in a further three; unidentified fungi were isolated in another nine cases. Fungal pneumonias occurred at a median age of 13·8 years (range 1·2–54·5 years). In four cases where *Aspergillus* species were isolated, the patients were receiving Itraconazole anti-fungal prophylaxis. *Staphylococcus* species, *Aspergillus* species and *Streptococcus milleri* were lung abscesses isolates, the latter organism not reported previously as pathogenic in CGD.

An organism was isolated in 31 (39%) of 79 liver abscesses; in 27 (88%) by fine needle aspiration or following surgical drainage. Fifteen patients were diagnosed consequent to a liver abscess. *Staphylococcus* species caused most liver abscesses and none were due to fungi. Liver abscesses were associated with septicaemia (five patients), pneumonia (six), bacteraemia (three) and lung abscesses (two).

Organisms were isolated in 59% of osteomyelitis: *Staphylococcal* species and *Aspergillus* accounted for 7 (70%); other causative organisms included *Neisseria meningitidis* (one), *Salmonella typhi* (one) and atypical mycobacteria (one). The organism causing septicaemia was isolated in 27 (71%) cases, *Staphylococcus* species, *Salmonella enteritidis* and *Acinetobacter junii* being the most common, with *Burkholderia* isolated only once. Ten patients experienced more than one episode of septicaemia; *Salmonella* and *Acinobacter* were the only organisms that recurred in the same patients. Perianal abscesses were common; 26 (28%) patients experienced 41 episodes, but organisms were rarely isolated. Two patients with XL disease (aged 16·6 and 17·3 years) had brain abscesses. In one patient *Aspergillus* species was isolated despite itraconazole prophylaxis with therapeutic drug levels. A further 183 abscesses at other sites with no known isolates occurred in 53 patients (43 XL, six AR) and led to the diagnosis in 19 patients. Organisms were isolated in 18% of 104 episodes of suppurative adenitis, the most common presenting feature of CGD; in all cases the organism identified was a *Staphylococcus* species. Thirty-six patients experienced 69 episodes of skin infections requiring antibiotic treatment. Non-infectious skin complications included vasculitis, granulomatous lesions, a lupus-like rash and photosensitivity (12 patients, 15 episodes).

Thirty-five (37%) patients (26 XL, seven AR) had colitis (median age of onset 5·2 years, range 0·01–41 years). Thirty

Table 2. Infectious complications in chronic granulomatous disease patients.

Infections	No. of patients			Median age years (range)	No. episodes	Organisms isolated
	XL	AR	UK			
Pneumonia	37	6	6	10·2 (0·2, 56·9)	105	48%
Suppurative adenitis	31	4	3	2 (0·2, 28·8)	104	18%
Liver abscess	20	5	2	14·3 (0·3, 38)	79	42%
Septicaemia	16	4	2	3·3 (0·4, 38·8)	38	71%
Osteomyelitis	8	3		10·8 (3·6, 30·3)	17	71%
Lung abscess	6	2	1	18·4 (1·6, 37·8)	16	38%

XL, X-linked; AR, autosomal recessive; UK, unknown.

Table 3. Organisms isolated.

	Pneumonia	Liver abscess	Lung abscess	Osteomyelitis	Renal infections	Septicaemia
Fungi						
Aspergillus	13	–	1	2	1	–
Suspected *Aspergilllus*	3	–	–	–	–	–
Fungi: not identified	9	–	–	–	–	
Staphylococcus						
Staphylococcus: not identified	1	9	2	2	–	3
S. aureus	4	17	–	3	–	3
S. epidemidis	1	1	–	–	–	4
Streptococcus						
Streptococcus: not identified	2	–	–	–	–	1
Strep. milleri	1	1	2	–	–	2
Strep. pyogenes	–	1	–	–	–	–
Pseudomonads						
Burkholderia cepacia	5	–	–	–	–	1
P. gladioli	–	–	–	–	–	1
Nocardia	2	–	–	–	–	–
Salmonella	–	–	–	1	–	8
Other	7	1	1	2	3	8
Multiple organisms per infection	0		1			4
Total number of patients affected (% of total cohort)	49 (52%)	27 (29%)	9 (10%)	11 (12%)	9 (10%)	22 (23%)
Total number of episodes	105	79	13	17	12	38
Number of episodes where organisms identified (%)	49 (47%)	31 (39%)	6 (46%)	10 (59%)	4 (33%)	27 (71%)
Unknown organism	56	48	7	7	8	11

(89%) patients had endoscopies, 80% had biopsies with granulomas reported in 63%, pigmented macrophages in 26% and eosinophilc infiltrate in 20%; there were no consistent histological features diagnostic of CGD. Oesophageal obstruction or stricture occurred in five patients and pyloric obstruction in a further six patients. All those with oesophageal, pyloric or small bowel obstruction were treated with steroids. Surgical intervention was required for two patients with upper gastrointestinal (GI) tract obstruction [balloon dilatation of the oesophagus (one), pyloromyotomy (one)]. Gingivitis, stomatitis, oral ulceration and oral abscesses were recorded in 23 (24%) patients, and gingival hypertrophy was recorded in a further six patients (6%).

Twenty-three (24%) patients had eye complications, nine (39%) having chorio-retinal abnormalities, three with obvious scars. Two other patients had scars but no chorioretinal abnormality. Six (26%) patients had at least one episode of keratitis. Nineteen (20%) patients developed renal problems (median age 10·4 years, range 0·3–45 years), including severe acute or chronic infection (eight patients), significant renal impairment (four), scarring (two) and abscesses (two). Seven patients had urogenital tract granulomas and four were treated with steroids.

Seventy patients (54 XL, 11 AR, five unknown inheritance) underwent a total of 312 surgical procedures to drain or excise abscesses, with a median age at first operation of 2·8 years. For the 1411 follow-up years this equates to one operation every 4·5 years.

Weight was recorded for most adults and children; only children had height recorded. At diagnosis, 75% of those whose height was measured were below the population mean, and 77% were below the mean for weight. Twenty-nine (31%) patients required nasogastric nutritional supplementation with or without parenteral nutrition, and four patients required total parental nutrition while hospitalized for an acute illness. Five patients (6%) received hormone therapy for poor or delayed growth.

Chronic respiratory disease was common. Of 30 patients who underwent high resolution computerized chest tomography, 23 (77%) had significant abnormalities: bronchiectasis in 10 patients (43%), obliterative bronchiolitis in three patients (13%) and chronic fibrosis in 10 patients (43%).

Surprisingly, complications were more common after diagnosis than before. Patients with XL CGD suffered from more episodes of pneumonia, although fewer episodes of septicaemia; colitis was more common in patients with XL CGD (Table 4).

At the time of data abstraction all patients received antibiotic prophylaxis: most received cotrimoxazole but trimethoprim, azithromycin, ciprofloxacin and rotations of antibiotic combinations were also used. Eighty-seven (93%)

Table 4. Complications pre- and post-diagnosis and mode of inheritance.[†]

Complication	Total person-years	Total pre-diagnosis person-years	Total post-diagnosis person-years	Rate per 1000 person-years (95% CI)	Ratio post/pre-diagnosis (95% CI)	XL total person-years	XL pre-diagnosis person-years	XL post-diagnosis person-years	AR total person-years	AR pre-diagnosis person-years	AR post-diagnosis person-years	Total ratio XL : AR (95% CI)
All abscesses	264	71	193	187 (165, 211)	1·75 (1·33, 2·33)	168	49	119	24	12	12	3·74 (2·43, 6·00)
Colitis	66	16	50	47 (36, 60)	2·01 (1·13, 3·79)	42	10	32	19	5	14	1·18 (0·67, 2·15)
Liver abscess	67	16	51	47 (37, 60)	2·05 (1·15, 3·86)	40	7	33	14	9	5	1·53 (0·81, 3·04)
Lung abscess/empyema	14	4	10	10 (5, 16)	0·62 (0·14, 2·15)	8	1	7	3	3	0	1·43 (0·34, 8·34)
Osteomyelitis	16	7	9	11 (6, 18)	0·83 (0·27, 2·62)	12	4	8	4	3	1	1·60 (0·49, 6·82)
Pneumonia	92	19	73	65 (53, 80)	2·48 (1·48, 4·35)	72	11	61	9	5	4	4·27 (2·13, 9·73)
Septicaemia	36	15	21	26 (18, 35)	0·90 (0·44, 1·88)	22	11	11	6	4	2	1·96 (0·77, 5·91)
Surgery	312	99	213	221 (197, 247)	1·39 (1·09, 1·78)	209	69	140	37	19	18	3·2 (2·12, 4·40)
Serious events exc. surgery	555	148	407	393 (361, 427)	1·77 (1·46, 2·15)	364	93	271	79	41	38	2·46 (1·93, 3·18)
All serious events	867	247	620	614 (574, 657)	1·62 (1·39, 1·88)	573	162	411	116	60	56	2·64 (2·16, 3·25)

[†]The mode of inheritance is not known for 50 pre- and 101 post-diagnosis person-years, therefore the addition of X-linked (XL) and autosomal recessive (AR) years does not equal the total; 95% confidence intervals (CI) were chosen as they include the real magnitude 95% of the time.

patients received anti-fungal prophylaxis, itraconazole in all, although ketoconazole and voriconazole had been used previously. Only two patients received interferon (IFN)-γ as continuous prophylaxis. However, 33 patients (35%) received IFN-γ during a total of 50 infective episodes, liver abscess (eight patients), GI disease (seven), sepsis (five) and fungal infection (four). Granulocyte infusions were given to 12 patients (13%) – for severe or resistant sepsis, including liver abscess (four patients), pneumonia (one), unspecified fungal infection (three), brain abscess (one) and osteomyelitis (one). Growth colony stimulating factor was used in 12 patients (13%), for colitis (one patient) or for severe infections including liver abscess (four), fungal infections (three) and pneumonia (two). Forty patients (42%) received systemic steroid treatment for colitis or GI obstruction. Three patients received intravenous steroids when severely ill. Topical steroid treatment was prescribed for severe eczema or lupus-like rashes. Steroid mouthwashes were prescribed commonly for mouth ulcers.

At the time data were abstracted, 12 (13%) patients had undergone haematopoietic stem cell transplantation successfully and one patient had undergone gene therapy.

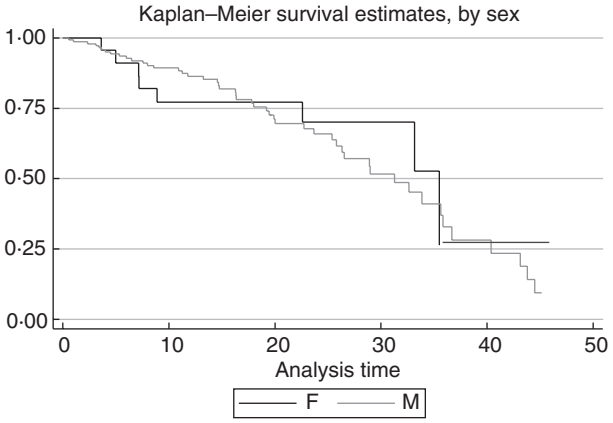
The mortality study identified 55 patients; 44 were identified by the Office of National Statistics search and 21 from contact with 115 physicians. Only 10 patients were identified by both methods. Age-specific mortality rates per million for each 5-year age band were calculated and there were no significant differences between them, ranging from 0·5 per million in the 5–9-year age group to 0·2 per million in the 20–24-year age group. Overall survival rates were 88% at 10 years, 73% at 20 years, 55% at 30 years and 28% at 40 years; for men these were 89%, 71%, 51% and 27% and for women these were 81%, 81%, 74% and 28% respectively.

Pneumonia and septicaemia were the most common cause of death. There were no significant differences in the cause of death across the different age groups. *Aspergillus* species accounted for 12 (50%) of the 24 cases (44%) where an organism was reported. Other isolates included unidentified fungi (16%), *Pseudomonas* (20%), *Staphylococcus* (8%) and *Nocardia* (1%); the latter occurred in the 10–14-year age group.

The survival curves (Fig. 2) showed overall survival of 88% at age 10, 73% at 20, 55% at 30, 28% at 40 and 12% at 50 and were broadly similar for men and women.

Discussion

This prospective study across the United Kingdom and Ireland has established a formalized reporting system, registering patients cared for in all settings. Cases were ascertained through multiple sources, making ascertainment as complete as possible. In other registry-based studies, information proformas were completed by specialists in participating centres [20–22]; in this study three designated researchers collected data, allowing for thorough and consistent data abstraction



Survival %	10 years (95% CI)	20 years (95% CI)	30 years (95% CI)	40 years (95% CI)	50 years (95% CI)
Overall	88 (82, 92)	73 (63, 80)	55 (43, 66)	28 (14, 43)	12 (3, 27)
Male	89 (82, 93)	71 (60, 79)	51 (37, 63)	27 (13, 44)	9 (2, 24)
Female	81 (57, 92)	81 (57, 92)	74 (47, 88)	28 (2, 67)	28 (2, 67)

95% confidence intervals were used as they include the true population 95% of the time

Fig. 2. Survival figures by sex. F, femal; M, male; CI, confidence intervals.

for all complications and infections. The birth prevalence in the United Kingdom and Ireland was 8·5 per million (95% CI 6·4–11·1 per million) and is twice that reported for the United States and Japan four times that of Sweden [20–22]; considerably higher than considered previously. As the northern European population is homogeneous and broadly similar to that of the United Kingdom and Ireland, and the proportion of XL and AR patients in northern Europe is similar to those in this study, there are no obvious reasons for the higher prevalence other than more rigorous case ascertainment. This is the first time that birth prevalence has been reported by gender and mode of inheritance. Disappointingly, despite increasing awareness of CGD, patients are not diagnosed significantly earlier than they were 3 decades ago. Men were diagnosed significantly earlier than women, even when excluding those diagnosed as a result of a positive family history. However, some men are still diagnosed late. Most cases were XL, who were diagnosed at an earlier age than AR, and tended to have more complications such as abscesses, suppurative adenitis and lung disease. Despite the widespread and early initiation of prophylactic anti-microbials (two-thirds of patients were diagnosed by 5 years of age), mortality remains high and suggests that by early adult life around 50% of patients had died; follow-up studies of the current cohort are needed to clarify this further.

Despite the use of prophylaxis, serious life-threatening bacterial and fungal infections remain common. Ten fungal infections occurred in eight patients receiving anti-fungal prophylaxis, in one patient despite documented itraconazole blood levels in the therapeutic range. Thus, it is unlikely that that poor compliance alone accounted for the persistence of serious infections. *Aspergillus* species, unidentified fungi and *Staphyloccal* species were the most common organisms isolated, in keeping with studies from the United States, Sweden, Iran and Italy [20,21,23,24]. However, there was a relative paucity of infections with Burkholderia, Nocardia and Serratia. Four of the patients who developed liver abscesses had suffered from other infections in the preceding weeks [perianal abscess (two patients) and suppurative adentitis (two)], highlighting the importance of haematological spread of organisms to the liver in CGD.

As described previously, GI disease was common in CGD [12–14]. In contrast to previous findings it appeared to be more common in AR patients than in those with XL, although this was not statistically significant [9,25]. Colitis or colitic symptoms were present in 15 patients prior to their diagnosis, highlighting the importance of gastroenterologists being aware of CGD and its manifestations. There was significant respiratory morbidity; 20 (21%) patients were hospitalized before the age of 5 years with pneumonia and 77% of those who had high resolution computed tomography had significant radiological abnormalities. Further studies are required to determine the aetiology of growth failure and chronic respiratory disease in these patients. In common with previous studies [9,19,26], anti-bacterial and anti-fungal prophylaxis in the United Kingdom and Ireland is used widely; 100% of patients received anti-bacterial and 93% of patients received anti-fungal prophylaxis. Of patients in the US registry 89% received antibiotic prophylaxis at some time, but no reference is made with regard to anti-fungal prophylaxis [21]. The use of IFN-γ as prophylaxis, however, was notably different [21,27]: 79% of patients in the United States compared with 35% of patients in the United Kingdom and Ireland. Granulocyte infusions were used comparably.

Previous studies comparing the clinical course of XL with AR disease have not resolved the debate as to whether XL disease is clinically more severe than AR disease. Our study, like others, found that XL patients presented significantly earlier. Because of the small number of patients with AR disease we have been unable to show statistically significant differences in the frequency of severe infections or inflammatory sequelae between XL and AR disease but patients with XL disease experienced more episodes of pneumonia and abscesses. More significantly in XL and AR disease, the rate of severe complications (inflammatory and infectious) increased following diagnosis, highlighting the importance of curative treatments, over prophylaxis.

Comparison of complications in patients with CGD across the world can now be attempted (Table 5). While caution is required in drawing too many conclusions, as the nature of the studies differed and data ascertainment was incomplete to a greater or lesser degree in the different

Table 5. Comparison of published registry data.

	% of infection†			% of documented episodes							
	No. of patients	Bacterial infection	Fungal infection	GI tract	Liver abscess	Lung infection	Perianal abscess	LN abscess	Septicaemia	Osteomyelitis	Death (Aspergillus)
USA§ [21]	368	81	19	n.a.	7	24	4	13	5	6	65 (27)
Japan¶ [22]	221	n.a.	n.a.	9	11	26	17	24	6	5	42 (12)
Sweden§ [20]	21	87	13	5	7	19	3	22	n.a.	4	3 (0)
UK¶††	94	70	30	8	18	28	9	24	9	4	55 (12)
Italy§ [24]	60	54	46	4	9	36	7	16	10	4	6‡ (3)
Spain¶ [28]	13	80	20	8	n.a.	11	n.a.	14	7	1	4 (1)

†Percentage of organisms isolated. ‡Two died from complications of bone marrow transplantation. §Longitudinal study. ¶Cross-sectional study; ††data from this study; n.a., information not available. Death refers to the number of deaths reported in the study, figures in brackets refer to those deaths associated with *Aspergillus* infection. GI, gastrointestinal; LN, lymph node.

studies, it is clear that lung complications and lymph node abscesses are the most common complications, and that infection with *Aspergillus* species is a significant cause of mortality in all parts of the world.

Mortality remains significant even at a young age and fungal infection remains an important cause of death. Contrary to previous studies that reported mortality rates improving in recent decades [19], this study showed that mortality remains severe across all age groups (27% at aged 20 years). Survival is reduced for men and women. This is surprising, as CGD was thought previously to be less severe in women; however, as there were fewer women than men, caution is required in interpretation of this finding. The survival curves for patients up to age 20 years are likely to be an accurate representation because the case ascertainment for this age group was as complete as possible; the rapid decline in survival after this age, and apparent mortality, may be due in part to missing cases and under ascertainment of some cases, despite the best attempts of this study. Indeed, our mortality rate may be an underestimate, particularly as those patients identified by physicians did not tally fully with those identified from death certificates and vice versa.

Chronic granulomatous disease was first described as 'fatal granulomatous disease of childhood' [1]. Since then advances in the management and treatment of these patients have led to an improvement in life expectancy. However, many still have a chronic disease, which results in prolonged episodes of hospital admission and debilitation [29]. Despite appropriate prophylactic anti-microbial treatment, probably up to 50% have died by middle adult life. CGD is a multi-faceted disease with a wide spectrum of disease severity. Patients may present to a variety of specialists, and it is vital to raise awareness of this condition, in order that appropriate treatment can be instituted promptly. We have established a detailed registry which we plan to maintain by prospective follow-up of known patients and ascertainment of newly diagnosed cases. The registry will become an increasingly valuable resource providing information on the natural history and sequelae of the disease. The ongoing morbidity and mortality argue for curative treatments. Haemopoetic stem cell transplantation is safe and effective in other immunodeficient patients, and was successful in six of 10 (60%) patients given T lymphocyte-depleted marrow after non-myeloablative conditioning, but in 25 of 29 (82%) patients given replete marrow, after fully myeloablative conditioning [30,31]. Gene therapy has shown significant transient benefits and future developments may also make this a viable curative treatment.

Acknowledgements

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Supplementary material

The following supplementary material is available for this article online:

Supplementary data. Calculation of adjusted birth prevalence.

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1365-2249.2008.03644.x
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