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Prognosis of chronic granulomatous disease

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Abstract

The records of 28 patients with chronic granulomatous disease born over a 32 year period were reviewed. The characteristics of the group, and the frequency with which various clinical and laboratory features had been recorded, was assessed. Nine patients were known to have died, in most cases of progressive suppurative infection. Actuarial analysis showed 50% survival through the third decade of life. The long term survival of patients developing symptoms after the end of the first year of life was significantly better than that of patients whose illness started in infancy. Our data confirm that the severity of chronic granulomatous disease is not uniform, and that the prognosis for long term survival is better than that suggested in earlier reports. Early onset may be a poor prognostic sign and invasive aspergillosis is a life threatening complication. In the absence of curative treatment, trials to assess the effectiveness of interferon gamma are necessary and early antenatal diagnosis should be offered to as many affected families as possible.

In 1957 Berendes, Bridges, and Good published a paper entitled 'A fatal granulomatosis of childhood. The clinical study of a new syndrome'.[1] Nine years later the same group showed that the syndrome was caused by an inborn inability of the patients' phagocytes to kill ingested microbes.[2] The salient features of lymphadenitis, superficial and deep abscesses, dermatitis, enlarged organs, and pneumonitis leading to chronic lung damage, were soon established.[3] Subsequent experience has shown that the condition is not universally fatal in childhood and that it affects predominantly, but not solely, boys.[4 5] The diagnosis is confirmed by performing the phorbol-myristate acetate stimulated nitroblue tetrazolium (NBT) test, which gives percentage values of stained neutrophils close to zero in affected cases, close to 100 in normal subjects, and intermediate (usually 20–80) in females heterozygous for the X linked form.

A defect of any one of the many potential sites in the metabolic pathways of the phagocytic respiratory burst could produce the chronic granulomatous disease phenotype and a number have been described. The commonest is a deficiency of a phagocyte cytochrome b seen in most cases of the more common X linked recessive form,[6] as a result of mutation in the gene for the larger β subunit of this haemoglycoprotein.[7 8] The gene has been mapped to the Xp21.1 region of the X chromosome and has been cloned.[9] Some patients with autosomal recessive, cytochrome b positive chronic granulomatous disease have an abnormality of one or a group of neutrophil cytoplasmic proteins, phosphorylation of which is thought to be concerned in the regulation of the oxidase mechanism of the respiratory burst.[10] This work has done much to increase the understanding of oxidative bactericidal mechanisms in normal phagocytes and provides a rational basis for the range of clinical severity seen in the chronic granulomatous disease phenotype.

No cure has yet been found for the disease. There has been a little experience with bone marrow transplantation and the results have shown at best partial success.[11–13] Palliation has been achieved with antimicrobial agents both as prophylaxis and for the treatment of infections as they occur. Retrospective studies have suggested that regular co-trimoxazole in particular improves the clinical course although no controlled prospective study has ever been done.[5 14] Antenatal diagnosis has only been made by carrying out the NBT test on fetal blood obtained at the late gestational age of 18–20 weeks.[15]

Important progress is now being made in all three of the areas of management mentioned above. Cure, in the form of somatic gene treatment, has not been achieved but is under investigation in several centres. Palliative treatment with interferon gamma is being studied; the cytokine has been shown in two small studies to ameliorate defective phagocyte function when given subcutaneously to some patients with both cytochrome b positive and cytochrome b negative chronic granulomatous disease.[16 17] Multicentre prospective controlled trials are currently in progress to assess whether the cytokine also confers clinical benefits. Finally, antenatal diagnosis by chorionic villous biopsy in the first trimester is now possible for the proportion of mothers that is informative for at least one of two polymorphisms within the X linked chronic granulomatous disease gene that have recently been described.[18 19]

This review was undertaken to record our clinical experience of this rare disease to date so that the information can be used as a guide in advising present and future patients and their families about the application of new interventions as they become available.

Methods

The records of our clinical immunology laboratory from 1964 to 1989 were reviewed and 38 patients were identified who had had abnormal

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NBT tests. Of these, 28 had been seen and followed up at our hospital and had adequate, traceable medical records; these formed the study group. All 28 had clinical histories suggestive of chronic granulomatous disease.

A proforma was designed to summarise demographic, clinical, family, laboratory, and follow up information and this was filled in from the hospital and laboratory records of each case. The data were analysed on a microcomputer, and Fisher's exact test was used to test the significance of differences between groups.

Results

DEMOGRAPHIC DATA

The patients were born over a 32 year period from 1955 to 1987. There were two sibling pairs, the remainder being unrelated. There were 26 boys and two girls. The racial pattern was predominantly white, reflecting that of our referral population.

ONSET AND DIAGNOSIS

The age at the onset of symptoms is shown in fig 1. In about half this was during the first year of life, and in 22 of 28 (79%) before the second birthday. The mean interval between onset and diagnosis fell with growing experience of the disease from 4·6 years in the 1960s to 1·5 years in the 1980s. Only two cases were diagnosed because they had positive family histories, both in the 1960s.

INHERITANCE (fig 2)

The two girls were presumed to have autosomal recessive inheritance. In both cases parental NBT tests were normal and one had confirmatory studies that showed a lack of phosphorylation of a 47 kDa cytoplasmic protein, but neither had affected siblings. Six boys whose mothers had normal NBT tests were designated 'autosomal or new mutation'. Seventeen boys whose mothers had abnormally low NBT test results were presumed to have X linked inheritance; six of these had pedigrees suggestive of this pattern. Two boys whose mothers had had abnormal bactericidal assays but no NBT tests done were designated 'probably X linked'; one of these also had a suggestive pedigree. One child had been adopted and no family data were available.

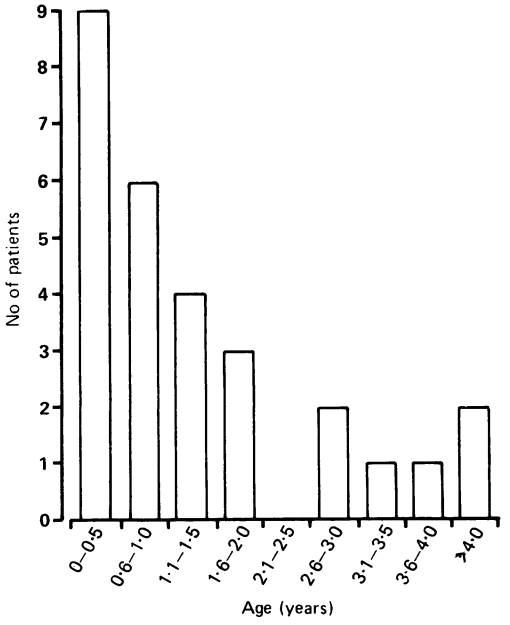

Figure 1 Age of onset of symptoms in 28 patients with chronic granulomatous disease.

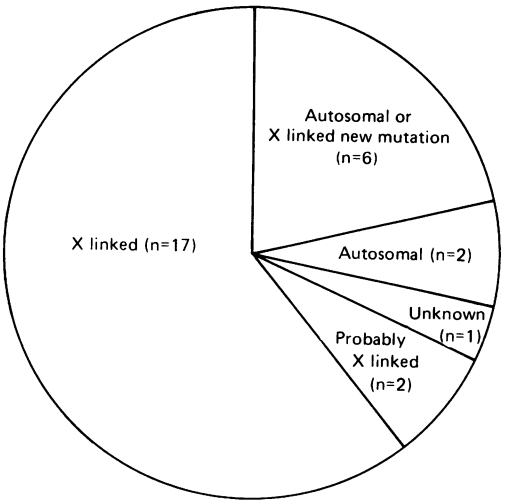

Figure 2 Inheritance pattern in 28 patients with chronic granulomatous disease.

CLINICAL AND LABORATORY FEATURES

The signs, symptoms, and complications recorded are summarised in table 1. Superficial abscesses, lymphadenitis and lymphadenopathy, recurrent fevers of unknown origin, chest infections, failure of growth, dermatitis, and enlarged organs were common features. A substantial minority developed invasive infection of bone, liver, or blood at some point. The recorded weights and heights at presentation were usually below the 50th centile and often low (fig 3). Nine of 24 patients (38%) were anaemic (haemoglobin concentration <100 g/l) and 11 of 20 (55%) were hypergammaglobuli-

Table 1 Clinical features recorded in 28 cases of chronic granulomatous disease. Figures are expressed as number (%) of patients

Common symptoms:	
Superficial abscesses and lymphadenitis	27 (96)
Persistent fever	20 (71)
Chest infections	17 (61)
Failure to thrive	15 (54)
Common signs:	
Lymphadenopathy	24 (86)
Dermatitis	23 (82)
Hepatomegaly	19 (68)
Respiratory signs	15 (54)
Splenomegaly	12 (43)
Uncommon features:	
Diarrhoea	5 (18)
Otitis	4 (14)
Gingivitis	3 (11)
Fungal nail infection	1 (4)
Aphthous ulcers	1 (4)
Invasive infections:	
Septicaemia	11 (39)
Osteomyelitis	10 (36)
Liver abscess	7 (25)
Brain abscess	2 (7)

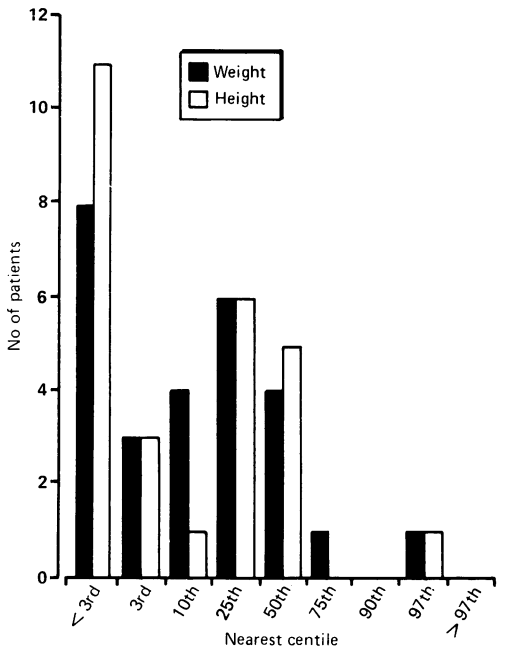

Figure 3 Nearest centiles at presentation in 27 patients with chronic granulomatous disease.

naemic at the time of presentation. In four families, a family history of systemic lupus erythematosus had been noted, and in two of these (and three others) the patients' mothers gave histories of photosensitive facial rash (discoid lupus).[20]

SURVIVAL

At the time of study, 16 patients were alive (five aged 0–9 years, five aged 10–19 years, and six aged 20–30 years, fig 4); nine had died, and three were lost to follow up. Six of the nine deaths were the result of progressive suppuration in the lung or other organs, or a combination. One patient died of liver failure after partial hepatectomy for a chronic liver abscess, one died during an exploratory laparotomy for intestinal obstruction, and one died of unknown cause having had bone marrow transplantation attempted seven years before. Most of the patients had received some form of antibiotic prophylaxis at some time, but there were inadequate data to correlate this with outcome.

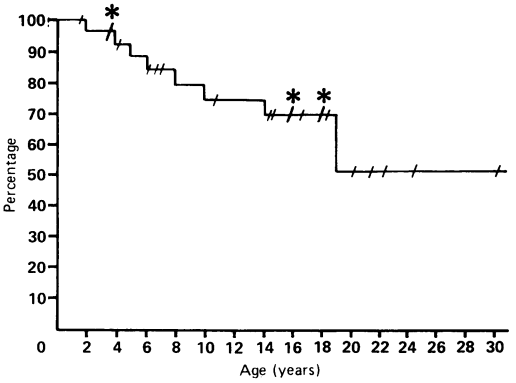

Figure 4 Actuarial survival curve for 28 patients with chronic granulomatous disease. Asterisks indicate a patient lost to follow up at that age.

Recent patients had consistently been given oral prophylaxis with co-trimoxazole.

Aspergillus infection occurred in eight patients. Three developed progressive infection of lung or bone, or both, and died; two of these received amphotericin. Two patients, one with an infected haematoma of the buttock and one with sternal osteomyelitis were still receiving treatment at the time of the study. Two patients, one with empyema and one with infection of the chest wall, were successfully treated. One patient was lost to follow up.

An actuarial survival curve was computed and is shown in fig 4. Six deaths occurred in the first decade of life and three in the second; six patients had survived into the third decade. There was more than 70% survival at 10 years of age, and 50% survival from 20 years of age onwards.

Discussion

As the clinical syndrome of chronic granulomatous disease is caused by a group of molecular disorders that lead to varying degrees of abnormality of phagocytic oxidative microbicidal function, it is to be expected that a range of clinical severity will be seen in patients with the disorder. Our experience certainly bears this out (fig 1, 3 and 4; table 1). A more mild clinical course among patients with the autosomal recessive cytochrome b positive type has been reported.[21] As in another recent report,[5] our series showed no apparent difference in clinical severity or mortality between the different inheritance groups (fig 2). We did not, however, have data on cytochrome b concentrations in our cases. It was of interest that the two female cases, who almost certainly have autosomal recessive type chronic granulomatous disease, both had illnesses of late onset (4 and 6 years), both are alive at the time of study (aged 7 and 22 years) and both have had relatively mild clinical courses with no growth failure, enlarged organs, or serious deep seated infection.

When patients who developed symptoms for the first time before their first birthday were compared with those who developed them later, a significant difference in the long term survival was found between the two groups (table 2). This suggests that onset in infancy may be an adverse prognostic indicator in chronic granulomatous disease.

Most previous reports have suggested a poor prospect of long term survival for children with chronic granulomatous disease,[3] although adults with the disease have been reported.[22]

Table 2 Long term survival correlated with age of onset in 17 patients with chronic granulomatous disease

	Alive and >14 years old	*Died before 14th birthday*
Onset before 1st birthday	2	6
Onset aged 1 or more	8	1
Totals	10	7

p=0·01.
The following were excluded: patients alive and <14 years old (n=6); those lost to follow up (n=3); and those who died after the age of 14 years (n=2).

One report of 48 paediatric patients showed a 50% survival rate maintained from 10 to 20 years of age.[5] Although there were some deaths in the second decade in our group, we have shown a similarly encouraging 50% survival rate extending into the third decade of life. The impression that chronic granulomatous disease is a 'less severe' disease now than when it was first recognised may in part reflect the use of prophylactic antibiotics and the diagnosis of less severely affected patients, but our data do show 50% long term survival rates among patients diagnosed in childhood more than 20 years ago.

Our patients were without exception troubled by recurrent or chronic symptoms, or both, and their lifestyles and those of their families were severely disrupted by the threat or occurrence of serious illness. The frequency of the various features and complications was comparable with that previously reported.[3-5] Although bacterial suppuration was the commonest infective problem, invasive infection with aspergillus carried a particularly high mortality when it occurred. The extreme difficulty of eradicating fungal infection in patients with chronic granulomatous disease, particularly when it affects the lungs or is disseminated, has previously been reported.[23]

In conclusion, this study confirms the main clinical features of chronic granulomatous disease, but suggests that there is reasonable hope of long term survival in paediatric cases. We intend to offer interferon gamma to patients with deep seated and unremitting infection, in particular that caused by *Aspergillus* spp. If current trials show that it is efficacious and safe, interferon gamma may also be offered prophylactically to patients who are well. Currently we offer first trimester antenatal diagnosis to known informative carriers of X linked chronic granulomatous disease, and second trimester diagnosis by fetal blood analysis to the remainder. Bone marrow transplantation is still a feasible therapeutic option if an HLA matched donor is available, but in time we hope that somatic gene treatment may become possible.

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