Increased mortality in cartilage–hair hypoplasia

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Abstract

***Background*—Cartilage–hair hypoplasia (CHH) is an autosomal recessive chondrodysplasia with severe growth failure and impaired immunity. Impaired immunity may result in increased mortality.**

***Aims*—To follow a cohort of 120 CHH patients for mortality from 1971 to 1995.**

***Methods*—The overall and cause specific disease mortality rates in patients with CHH, and the disease mortality rate in 194 parents and 158 non-affected sibs were compared with the national rates.**

***Results*—During follow up seven disease related deaths were observed versus 0.8 expected (standardised mortality ratio 9.3, 95% confidence interval 3.7 to 19). In most cases, the deaths were confined to the younger age groups and associated with defective immunity. The mortality of the parents and the non-affected sibs was similar to that in the general population.**

***Conclusion*—The study confirms increased mortality in patients with CHH attributable to defective immunity, especially in children.**

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Cartilage–hair hypoplasia (CHH) is a homogeneous autosomal recessive metaphyseal chondrodysplasia characterised by severe short limbed short stature (adult height 110–135 cm) and hypoplastic hair.[1 2] Most of the patients present with impaired cellular immunity, indicated by lymphopenia, decreased delayed hypersensitivity, and impaired in vitro responsiveness of lymphocytes to mitogens.[3] In addition, a significant proportion of patients have defective humoral immunity characterised by a deficiency of IgA or IgG subclasses or a combination of these.[4] The impairment of immunity leads to an increased rate of infections[3 4] and malignancies.[5] The defective erythropoiesis caused by impaired stem cell proliferation presents usually as mild macrocytic anaemia, but occasionally as severe hypoplastic anaemia of childhood.[2] The incidence of Hirschsprung's disease is increased.[2] These variable manifestations probably result from a generalised dysregulation of cellular proliferation.[2 6] The genetic defect has been assigned to chromosome 9p13 but the biological function of the CHH gene remains unknown.[7]

As the impaired immunity, defective erythropoiesis, and high incidence of Hirschsprung's disease may result not only in increased morbidity but also in increased mortality, we have followed a cohort of 120 CHH patients through the Finnish Population Register for disease mortality. We have compared the mortality rate of these patients with the mortality of the Finnish population and the mortality rate in the phenotypically healthy gene carriers—that is, the parents (all are healthy gene carriers) and the non-affected sibs (two out of three are gene carriers) of the CHH patients.

Materials and methods

Patients with CHH were identified through two thorough epidemiological surveys carried out in Finland in 1974[8] and in 1986.[9] Since 1986 we have received information on all CHH patients diagnosed in Finland; they were also included in the cohort. The affected sibs of these basic cohort members (probands) were identified through family search. The diagnosis of CHH was based on short limbed short stature, generalised laxity of joint ligaments, generalised metaphyseal flaring and irregularities in childhood radiographs, and genealogy compatible with autosomal recessive inheritance.[1 2] Hair hypoplasia was used only as a positive criterion.[2] The follow up of the probands started from the date of the epidemiological survey through which they had been ascertained, or, for the patients diagnosed since 1986 and for all affected sibs found through family search, from the date of diagnosis. The parents and non-affected sibs were identified through the Population Register. Their follow up for mortality started at the date of birth (sibs), at the birth of the index CHH patient (parents), or on 1 January 1971, whichever was later. The follow up of the CHH patients, their sibs, and parents ended at death or on 31 December 1995, whichever occurred first.

The cohort was compared with the Population Register Center of Finland, and the correct personal identification number (ID) and vital status were achieved for every cohort member. Since 1 January 1967 all residents of Finland have had a unique personal ID which is used in all main registers in Finland. Using these IDs, the causes of death were obtained from Statistics Finland. The national mortality rates (by year, sex, age, and cause of death) needed for calculating expected numbers of death were achieved from the same source.[10] Cause specific analyses were made for infectious diseases and haematological malignancies selected a priori because of the impaired immunity in CHH.

To calculate the SMR, the observed number of deaths was divided by the expected number of deaths. The exact 95% confidence intervals (CI) are given on the presumption that the number of observed cases followed a Poisson distribution.

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*Table 1 Number of patients with CHH and their relatives during follow up (N) and number of person years (PY) in 1971–1995, by age**

	CHH patients		Sibs		Parents	
Age	N	PY	N	PY	N	PY
0–4	53	140	80	328	—	
5–9	16	176	16	354	—	
10–14	20	208	15	360	—	
15–29	17	523	30	1002	66	265
30–44	8	262	15	661	96	1364
45+	6	63	2	383	32	1451
Total	120	1372	158	3088	194	3081

*For N the age at the beginning of follow up; for PY the dynamic age at follow up.

Results

PATIENTS WITH CHH

There were 50 men and 70 women in the CHH cohort (probands and affected sibs combined). The numbers of person years were 638 and 735, respectively (table 1). The mean length of the follow up of a person was 11.4 years.

During follow up, seven disease related deaths were observed; the expected number was 0.8 (table 2), the disease mortality in ages 0–14 being 21-fold the mortality of the Finnish population of same age. In children under 15 years of age there were three deaths caused by pneumonia (ages 3 weeks, 2 years, and 8 years; the standardised mortality ratio (SMR) for pneumonia in all ages was 160, 95% CI 34 to 470) and two deaths were caused by other infections: septicaemia (age 1 year) and encephalitis (age 13 years) (table 2). The septicaemia was caused by *Candida albicans*; the aetiology of the other infections remained unknown. In the older age group there were two deaths caused by non-Hodgkin's lymphoma (ages 22 and 45 years; the SMR for haematological cancer in all ages was 52, 95% CI 6.3 to 190; table 2). There were no national reference rates available for non-Hodgkin's lymphomas alone, but based on experience of the Finnish Cancer Registry, lymphomas comprise about two thirds of the deaths among the haematological cancers. Thus the SMR for non-Hodgkin's lymphoma alone would be approximately 80. In addition, there were two accidental deaths (ages 42 and 24 years; SMR 3.8, 95% CI 0.5 to 14).

SIBS

The cohort of unaffected sibs consisted of 158 persons with 3088 person years of follow up (mean length of follow up 19.5 years; table 1). During follow up, five deaths were observed, the expected number being 5.1 (SMR 1.0, 95% CI 0.3 to 2.3).

Table 2 Observed (Obs) and expected (Exp) disease mortality and standardised mortality ratios (SMR) with their 95% confidence intervals (CI) among 120 Finnish patients with CHH in 1971–1995

Age	Disease mortality	Obs	Exp	SMR	95% CI
0–14 years	All causes	5	0.24	21	6.8–49
	Pneumonia	3	0.004	680	140–2000
	Other infections	2	0.006	340	42–1200
15+ years	All causes	2	0.51	3.9	0.5–14
	Hematological cancers	2	0.04	52	6.3–190
Total	All causes	7	0.8	9.3	3.7–19

PARENTS

There were 194 parents included in the study. Parents who had died before 1971 did not contribute person years to this follow up. The mean length of follow up was 15.9 years (total person years 3081; table 1). The overall mortality of the parents was comparable with that in the general population (21 deaths observed versus 23 expected; SMR 0.9, 95% CI 0.5 to 1.3).

Discussion

The clinical characteristics of CHH were originally outlined in a study of 77 patients among the Old Order Amish, a religious sect in the United States.[1] The association of CHH and defective immunity was suspected because of severe attacks of varicella among these patients.[1] The deficiency of cell mediated immunity was confirmed in subsequent studies.[3 6] In a retrospective analysis of cellular immunity in 35 Finnish CHH patients, the lymphocyte stimulation indices were subnormal in 83% of the patients, and 57% had a decreased CD4+ cell count with a decreased total count of T lymphocytes and a subnormal CD4+/CD8+ cell ratio.[3] The B lymphocyte count was usually normal. A significant proportion of patients also have defective humoral immunity: in an unselected cohort of patients with variable history of infections, we observed a deficiency of IgA or IgG subclasses or a combination of these, in 35% of patients.[4] Impaired immunity leads to an increased rate of infections, especially respiratory tract infections, and to an increased rate of malignancies.[4 5] Furthermore, as confirmed by the present study, the defective immunity results in increased mortality among CHH patients.

The follow up of the cohort members for death is complete for the period of this study. SMR calculations had to be restricted to the period 1971–1995 because cause specific population mortality rates were available in a comparable way only for that period. After this period we have knowledge of three more deaths among the CHH cohort (at ages 14, 41, and 58 years as a result of septicaemia, non-Hodgkin's lymphoma, and pneumonia, respectively). These deaths provide further evidence of increased overall mortality, and especially excessive mortality caused by deficient immunity.

Mortality among the parents and the healthy sibs was similar to that of the normal population. Thus, the carriers of the CHH gene do not appear to have an increased overall mortality.

The impact of other skeletal dysplasias on life expectancy is variable: some forms are always lethal,[11] whereas in others the life expectancy may be normal. Standardised mortality ratios have previously been published only for achondroplasia, as studied in a cohort of 733 achondroplastic individuals.[12] Mortality was increased at all ages (SMR 2.3). Sudden death, usually caused by brain stem compression, accounted for the excess deaths in young children, and central nervous system, respiratory, and cardiovascular causes, in older children and in adults. The skeletal character-

istics in achondroplasia (restriction of the foramen magnum and stenotic spinal canal) are the main factors contributing to the increased respiratory and neurological mortality.[12] Increased mortality as a result of fractures has been observed in severe forms of osteogenesis imperfecta,[13] but population based mortality ratios are not available. Knowledge of life expectancy would be appreciated by the patients and the parents of an affected child. Disease specific mortality ratios would also give guidelines for supportive and prophylactic treatments, which may help to shift the life expectancy towards that of the general population.

In conclusion, the present study confirms an increased overall mortality rate attributable to defective immunity in patients with CHH. Mortality is especially high in children, but remains increased in older age groups.

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