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Cartilage-hair hypoplasia – clinical manifestations in 108 Finnish patients

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Abstract. Cartilage-hair hypoplasia is an autosomal recessive metaphyseal chondrodysplasia with short-limbed short stature, hypoplastic hair, and defective immunity and erythrogenesis. We have analysed the clinical outcome of 108 Finnish patients. Birth length was below −2.0 SD in 70% of the patients; the adult heights ranged from −11.4 SD to −5.2 SD. The sitting height percentage was increased in all but 4 patients. Six patients had normal hair. Increased ligamentous laxity was present in 95%, limited extension of the elbows in 92%, increased lumbar lordosis in 85%, thoracal deformity in 68%, genu varum in 63% and scoliosis in 21% of the patients. Defective cellular immunity had been observed in 88% and increased susceptibility to infections in 56% of the patients. Six patients had died of primary infections. The incidence of malignancies was 6%. Childhood anaemia had occurred in 79% of the patients. It was usually mild, but severe in 14 patients. Hirschsprung disease had been observed in 8, anal stenosis in 1 and oesophageal atresia in 1 patient. The intrafamilial variation of the syndrome was considerable as studied in 16 sibships.

Key words: Cartilage-hair hypoplasia – Metaphyseal chondrodysplasia – Clinical manifestations – Short stature – Immunodeficiency

Introduction

Cartilage-hair hypoplasia (CHH) is an autosomal recessive metaphyseal chondrodysplasia characterised by short-limbed short stature and hypoplastic hair [22]. Impairment of cellular immunity is indicated by lymphopenia and decreased in vitro lymphocyte reactivity; humoral immunity is intact [28, 39]. Deficient erythrocyte production often presents as mild transient macrocytic anaemia, and, on occasion, as congenital hypoplastic anaemia [18]. CHH is more common among Finns [12, 16] and among the Old Order Amish in the United States [20, 22] than in other populations; sporadic cases have been reported from other countries.

The main clinical characteristics of the disorder were originally outlined in a study of 77 Amish patients [22]. We now describe the spectrum of clinical features and associated complications as well as intrafamilial variability in 108 Finnish patients. A detailed analysis of their growth is available [17].

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Abbreviations: CHH = cartilage-hair hypoplasia; PHA = phytohaemagglutinin

Patients and methods

A recent epidemiological study of CHH in Finland revealed 107 patients [16]; since then five more patients have been ascertained. Four patients, three females and one male from three families, were excluded from the present study. Three of them lived in Sweden, and adequate information on their clinical outcome was not obtained. The fourth patient, a sister of an affected male, died neonatally of asphyxia and chondrodystrophy; no additional data were available. Thus, the final series consisted of 108 Finnish CHH patients, 46 males and 62 females from 88 families; in 12 families there were two affected siblings and in four families, three affected siblings. Sixteen patients had died. The living patients ranged in age from 10 months to 52 years (median 20 years). The diagnosis was based on short-limbed short stature, generalised laxity of joint ligaments, generalised metaphyseal flaring and irregularities in childhood radiographs, and compatible genealogy. Hair hypoplasia was used only as a positive criterion.

Eighty-seven of these patients, 37 males and 50 females, were clinically evaluated by one of us at the age of 3 months–49 years (median 14 years). Patients were carefully measured and the results compared to Finnish norms [19, 35]. Hair hypoplasia was rated as severe if hair was sparse and thin by inspection, and mild if hypoplasia was perceived only by touch. Extension of elbows was measured and rated as markedly limited if it was $> 25°$, mildly limited if 5°–25°, and normal if $< 5°$. Ligamentous laxity of the fingers and knees was clinically rated as marked, mild or normal. The chest was inspected for the presence of Harrison grooves, sternal prominence, asymmetry or other deformities. Lumbar lordosis and genu varum were evaluated on weight bearing and clinically rated as marked, mild or normal. Scoliosis was considered mild if the curvature was 10°–30° and severe if it was $> 30°$. Curves $< 10°$ were considered normal.

Hospital and health centre records of birth, medical history, growth, vaccinations and laboratory studies were collected for each patient. The records were reviewed for infectious diseases, abnormal haemoglobin levels and white blood cell counts, orthopaedic complications and procedures, and intestinal and other diseases. Susceptibility to infections was considered moderately increased if the patient had over a year had more than six uncomplicated upper respiratory tract infections or three or more protracted purulent infections, such as otitis or sinusitis. If the numbers were considerably higher, the susceptibility was regarded as severe. The degree of immunodeficiency was additionally classified on the basis of in vitro responsiveness of lymphocytes to phytohaemagglutinin (PHA); responses were considered severely subnormal if they were < 30% of normal mean, and mildly subnormal if 30%–60% of normal mean. Responses > 60% were considered normal. Anaemia was considered mild if Hb was below the 3rd percentile on age- and sex-adjusted reference values [3, 4] but > 80 g/l, and severe if Hb was ≤ 80 g/l. Lymphocyte and neutrophil counts below the 5th percentile for age and sex were considered subnormal [4].

Chi-square test was used for statistical analysis. The study was approved by the ethical committee of the Children's Hospital.

Results

Birth records

Fourteen of 100 (14/100) patients (14%) were born before 38 weeks of gestation (range 32–37 weeks) and 17/81 patients (21%) in breech position (the data were not available for 8 and 27 patients, respectively). The mean length and weight at birth, extrapolated to term [27], were 45.8 cm ± 2.8 cm (mean ± SD) ($n = 41$) and 3360 g ± 410 g ($n = 42$) for boys and 44.8 cm ± 2.7 cm ($n = 55$) and 3190 g ± 430 g ($n = 56$) for girls. The mean relative values (deviations in SD units from mean values for age and sex) for length and weight at birth [27], were − 3.0 SD (range − 7.3 SD to + 0.5 SD, $n = 96$) and − 0.8 SD (range − 3.7 SD to + 1.1 SD, $n = 98$), respectively. Relative birth length was below − 2.0 SD in 70% of the patients. In 32/42 children (76%) the shortness of limbs and/or stature had been noticed neonatally, and in 41/42 children (98%) by the age of 1 year.

Clinical features

At the time of the clinical examination all the patients were short for age, from − 11.8 SD to − 2.1 SD (median − 6.2 SD) (Figs. 1,2). Two patients were above − 3.0 SD. One of them was − 2.1 SD (57.5 cm) at the age of 3.5 months but − 4.4 SD (73 cm) at 22 months. The other had been − 3.0 SD but reached − 2.3 SD (151.7 cm) during pubertal growth spurt; his relative sitting height percentage was 4.1 SD. The 26 adult patients ranged from − 11.4 SD to − 5.2 SD (from 103.7 cm to 140.0 cm).

The growth failure was usually disproportionate with increased relative sitting height percentage (median

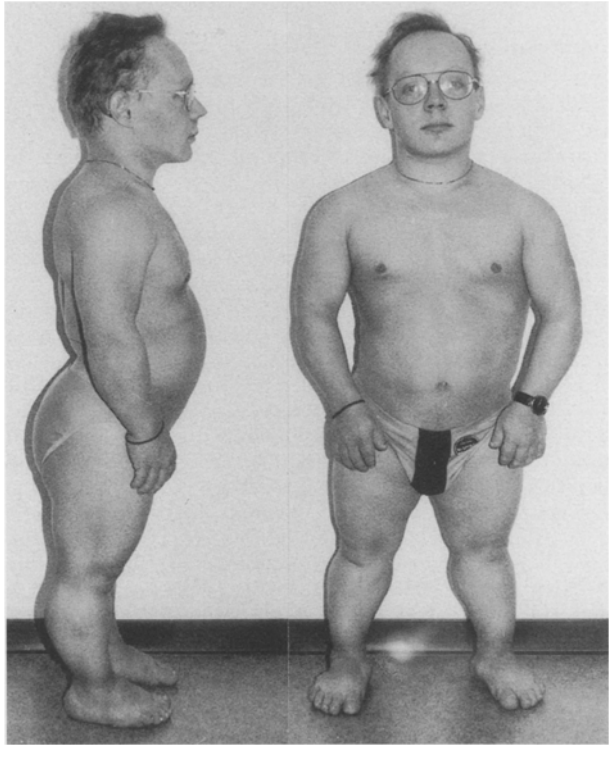

Fig. 1. A 26-year-old male with CHH. Note the short stature (height 110.7 cm), short limbs (relative sitting height-% + 11.0 SD), sparse hair, extension limitation at elbows, and increased lumbar lordosis. Varus deformity of the lower limbs had been corrected surgically 10 years earlier

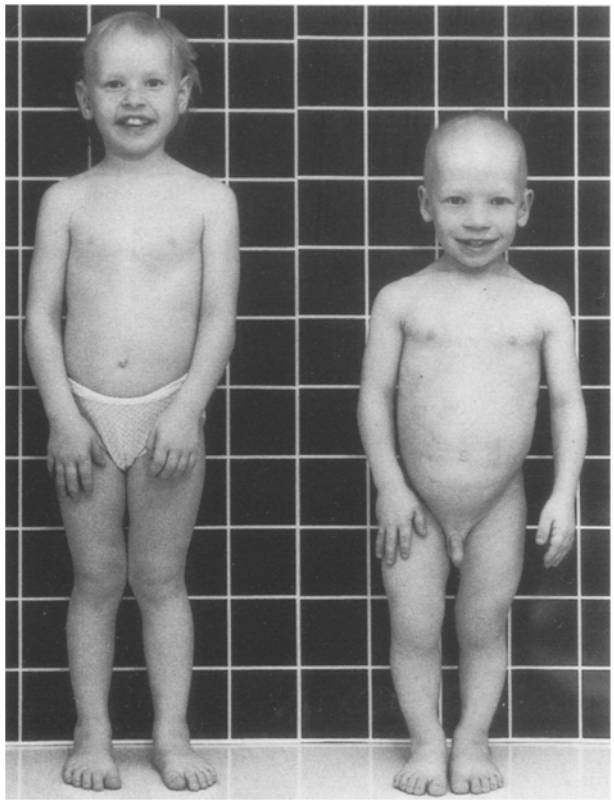

Fig. 2. Affected sibs: an 8-year-old girl (height 103.2 cm) with a 15 months older brother (height 89.4 cm) (patients II and I of sibship 1 in Table 4). Note the considerable variation of phenotype. Both patients had a hearing aid because of recurring otitis media and persisting perforations of the tympanic membranes

Table 1. Intrafamilial variation of the clinical findings among four sibships

Finding	Sibship 1			Sibship 2		Sibship 3		Sibship 4	
	I	II	III	I	II	I	II	I	II
Relative birth length (SD)	−5.1	−1.5	−1.7	−3.4	−0.6	−1.7	−3.4	−1.2	−1.7
Relative height at 2–6 years (SD)	−7.8	−5.2	−4.6	−7.0	−4.7	−3.2	−4.8	−3.7	−3.7
Adult relative height (SD)	?	?	?	−9.8	−7.9	−5.6	−6.5	−6.0	−7.2
Hair hypoplasia	+++	++	+	+++	+	+	++	+++	No
Increased infections	+++	++	+	+	No	+	++	+	No
Impaired lymphocyte proliferation[a]	++	++	+	+	+	No	+	+	No
Hirschsprung disease	Yes	No	No	No	No	No	No	No	No
Childhood anaemia	++	+	+	+	No	+	+	No	No
Extension limitation at the elbows	+	++	+	+	++	No	+	+	+
Ligamentous laxity	++	++	+	+	++	+	+	++	+
Genu varum	No	No	No	++	++	+	No	No	+

+ mild; ++ severe; +++ extremely severe

[a] In vitro responsiveness of lymphocytes to PHA

+ 5.8 SD) (Fig. 1,2). However, the relative sitting height percentage was normal (within 2.0 SD of normal mean) in 4 patients (from + 0.3 SD to + 1.9 SD), whose relative heights ranged from − 3.6 SD to − 5.0 SD. Three of them had deficient and 1, normal cellular immunity. One of them (sib III of sibship 1, Table 1) had two sibs with disproportionate CHH.

Of the patients 93% had hypoplastic hair (Table 2, Figs. 1,2). The clinical variation was great. Twelve patients (14%) were bald. Six patients (7%) had normal hair. Three of them had a sibling and one, another relative with all features of the syndrome. Two patients without positive family history had relative heights of − 4.9 SD and − 8.0 SD, metaphyseal changes typical of CHH in childhood radiographs, and severely decreased in vitro lymphocyte proliferative response to PHA.

The extension of elbows was limited in 92% of the patients (Table 2). Ligamentous laxity was observed in 95%, and chest deformity in 68%. Bowing of the lower limbs was usually mild. Lumbal lordosis was increased in most of the patients. Scoliosis was present in 21% and was usually mild (Table 2).

Immune deficiency

Of the patients 56% had been unusually prone to infections, half of them severely (Table 3). Continuous antibiotic prophylaxis for at least 6 months had been administered to 4 children because of recurrent severe respiratory infections. Six patients had died of primary infections (Table 4). On the other hand, 44% of the patients had shown no unusual susceptibility to infections even though deficient cellular immunity had been confirmed in half of them.

Frequent middle ear infections had necessitated adenoidectomy in 24 (22%) and installation of middle ear ventilation tubes in 17 (16%) patients. Recurrent sinusitis had required antrostomy in 5, and Caldwell-Luc operation in 4 patients. Nasal polyps had been operated in 5, and a vocal cord polyp in 1 patient. Tonsillectomy had been performed in 5 patients.

Table 2. Clinical features in 87 CHH patients

Feature	No. of patients	(%)
Hair hypoplasia	81/87	93%
Severe	48/87	55%
Mild	33/87	38%
No hypoplasia	6/87	7%
Limited extension at the elbows	79/86	92%
<25°	24/86	28%
5°–25°	55/86	64%
No limitation	7/86	8%
Ligamentous laxity	81/85	95%
Marked	49/85	58%
Mild	32/85	38%
No laxity	4/85	5%
Chest deformity	57/84	68%
Harrison's grooves	32/84	38%
Prominent sternum	28/84	33%
Narrow thorax	34/84	40%
Asymmetry	5/84	6%
Varus deformity of the lower limbs	54/86	63%
Marked	17/86	20%
Mild	37/86	43%
No deformity[a]	32/86	37%
Increased lumbar lordosis	72/85	85%
Markedly increased	17/85	20%
Moderately increased	55/85	65%
Not increased	13/85	15%
Scoliosis	18/86	21%
Severe	1/86	1%
Mild	17/86	20%
No scoliosis	68/86	79%

[a] Includes four patients whose varus deformity had been corrected with osteotomy and two patients with mild valgus

Severe varicella with widespread and prolonged skin manifestations and high fever had been reported in 35/56 (63%) patients with positive history of varicella. Several permanent scars had been observed in 15 of them. Se-

Table 3. Associated findings in 108 CHH patients

Finding	No. of patients	(%)
Increased infections	58/103	56%
Severely increased	30/103	29%
Moderately increased	28/103	27%
Not increased	45/103	44%
In vitro immunodeficiency[a]	53/ 60	88%
Severe	37/ 60	62%
Mild	16/ 60	27%
No immunodeficiency	7/ 60	12%
Childhood anaemia	67/ 85	79%
Severe	14/ 85	16%
Mild	53/ 85	62%
No anaemia	18/ 85	21%
Malignancies	6/108	6%
Haematological	1/108	1%
Skin neoplasms	3/108	3%
Other	2/108	2%
Gastro-intestinal complications	19/108	18%
Aganglionic megacolon	8/108	7%
Severe obstipation	5/108	5%
Anal stenosis	1/108	1%
Other	5/108	5%
Orthopaedic operations	17/108	16%
Corrective osteotomy	15/108	14%
Other	2/108	2%

[a] In vitro responsiveness of lymphocytes to PHA

Table 4. Age and cause of death of 16 deceased patients

Age at death	Cause of death
2 weeks	Hirschsprung diesease
2 weeks	Congenital aplastic anaemia, septicaemia
3 weeks	Asphyxia
3 weeks	Hirschsprung disease, pneumonia
3 months	Congenital hypoplastic anaemia, bronchopneumonia
6 months	Congenital hypoplastic anaemia
18 months	Septicaemia, haemo-phagocytic syndrome
21 months	Chronic necrotising enterocolitis
2 years	Pneumonia, colitis
8 years	Pneumonia
10 years	Lymphoma
13 years	Tuberculosis
13 years	Encephalitis
22 years	Lymphosarcoma
24 years	Accident
42 years	Accident

vere complications had not occurred. Two patients had been hospitalised because of severe varicella. One patient had had herpes zoster.

The infectious problems were most pronounced in early childhood. However, four female patients aged 22, 36, 51 and 51 years had considerable problems even in adulthood. Two of them had asthma, recurrent pneumonia and bronchiectasis. Lobectomy had been performed in one of them. Recurring sinusitis had required Caldwell-Luc operation in all four of them. Two of them had chronic otitis media. None of the other 45 adults were unusually susceptible to infections, though 23 had a history of recurrent infections in childhood.

Lymphocytopenia had been observed in 51/79 (65%) patients and neutropenia in 21/79 (27%) patients during childhood. In adults these were observed only occasionally. Impaired lymphocyte proliferation response to PHA had been observed in 88% of the patients studied (Table 3).

Live vaccines had been administered to most of the patients: BCG to 90, smallpox vaccine to 26, and measles-mumps-rubella vaccine to 29 patients. No unusual reactions had occurred; local infection had been reported in 2 patients after BCG and in 2 patients after smallpox vaccination.

Anaemia

Of the patients 79% had been anaemic during childhood (Table 3). Anaemia had usually been mild and subsided spontaneously before adulthood. However, 14 patients (16%) had had severe anaemia, which in all but 1 required red blood cell transfusions. Eight of them had recovered spontaneously by the age of 3 years. Four anaemic patients died of secondary infections and 1 patient of complications of surgery for Hirschsprung disease. In 1 patient severe anaemia had been secondary to a *Candida* sepsis and haemo-phagocytic syndrome; she died pancytopenic at the age of 18 months.

Malignancies

Six patients (6%) had a history of malignancy. Pulmonary lymphoma had been diagnosed in a female patient, who had had recurrent respiratory infections and progressive dyspnoea; she died at the age of 10 years. Another female patient presented with recurrent melena and haematemesis at the age of 22 years. Laparatomy revealed intestinal lymphosarcoma and the patient died 3 months later. Another patient was operated on for malignant testis tumour (progonoma) at the age of 6 months. Skin carcinoma had been observed in three patients aged 33, 35 and 48 years: basal cell carcinoma of the scalp and intraepithelial carcinoma of the cheek in one, basal cell carcinoma of the scalp in the other, and multiple basal cell carcinomas of the face, back and chest in the third.

Gastro-intestinal manifestations

Aganglionic megacolon (Hirschsprung disease) had been observed in two female and six male patients. In five of them the aganglionic segment was rectosigmoid, in two the whole colon distal to the hepatic flexure and in one the entire colon. The treatment had always been operative. Two of them had died of complications in the neonatal period. Another patient had had an anal stenosis. Five other patients had had chronic constipation in childhood, one of them with recurring rectal pro-

Table 5. Correlation between severity of growth failure and other manifestations of CHH

Manifestation	Severe growth failure[a]		Mild growth failure[b]		*P*
	Patients	(%)	Patients	(%)	
Severe hair hypoplasia	16/21	76	10/26	38	<0.05
Severely increased infections	11/23	48	5/26	19	<0.05
Severely impaired lymphocyte proliferation[c]	10/12	83	9/19	47	NS
Lymphocytopenia	13/18	72	8/22	36	<0.05
Neutropenia	8/18	44	3/22	14	<0.1
Severe anaemia	10/23	43	1/23	4	<0.01
Hirschsprung disease	5/28	18	0/26	0	<0.1

[a] Height below the 25th percentile on CHH-specific growth charts [22]
[b] Height above the 75th percentile on CHH-specific growth charts [22]
[c] In vitro responsiveness of lymphocytes to PHA

lapse. One infant had been operated for oesophageal atresia and another, for ileocecal invagination. One child presented with malfixation of the stomach. Gastro-oesophageal reflux had been confirmed in two patients, one of them had a small hiatal hernia. Three patients had been operated for inguinal hernia (bilateral in one case) and one, for umbilical hernia.

Duodenal biopsy had been performed in 35 patients. The finding was normal in all but 2 patients, who had very mild changes of the mucosa. Gliadin antibodies had been present in 8/61 (13%) patients; duodenal biopsy had been performed in two of them with normal result. Antibodies had been observed against cow's milk in 14/63 (22%) patients but clinical signs of cow's milk allergy in only 1 of them; she had been on soy milk until the age of 2.5 years.

One patient had persisting severe diarrhoea from the age of 3 months and she died of sepsis in extreme malnutrition 18 months later. Autopsy revealed chronic necrotising enterocolitis; the infective agent could not be identified. Another child had had symptoms suggesting malabsorption after surgery for Hirschsprung's disease; he died 8 months later. Autopsy revealed pneumonia and colitis, and bacterial cultures of blood and spinal fluid grew enterococci. One patient suffered from an intestinal amoebiasis over 2 years after a visit to Turkey. Two others had a severe *Clostridium difficile* gastroenteritis following antibiotic therapy.

Orthopaedic problems

Three patients had had congenital bilateral dislocation of the hips and one, congenital subluxation. One of them died neonatally. In the others the dislocation had been corrected conservatively. Two patients, a male of 9 years and a female of 14 years, had developed Legg-Perthes disease of the femoral head. Arthralgia was only occasionally reported in children. Of the adults 21/44 (48%) complained mild to moderate and 6/44 (14%), severe arthralgic pains, usually at the knees, ankles or lumbar region of the spine.

Corrective osteotomy because of genu varum had been performed in 15 patients from the ages of 3 years to 51 years (median 13 years). One patient had been operated on for a loose fragment in the elbow joint and another for recurrent dislocation of the patella.

Neurological complications

One patient had congenital unilateral facial nerve palsy with a rudimentary auricle on the same side. Idiopathic unilateral facial nerve palsy had occurred in two patients and sudden anosmia in another.

Three patients had had febrile seizures in childhood. Four patients had had seizures unrelated to fever. In one of them the seizures were regarded as breath-holding spells. In another, focal seizures evolving to grand mal began at the age of 22 years. He did not allow medical investigation of these seizures. The third patient presented with seizures characterised by absence and myoclonic movements at the age of 13 years. The seizures started 1 month after commencement of growth hormone therapy but did not diminish after cessation of the therapy. EEG revealed abnormal activity of the right temporal area, CT scan was normal. With carbamazepine the attacks diminished during a 3-year follow up. In the fourth patient symptoms characteristic of psychomotor epilepsy started at the age of 12 years. The attacks gradually increased and the state of consciousness declined. CT scan of the brain as well as cytology and histology of a brain biopsy were compatible with infection, but no infectious agent could be identified. The patient died 21 months later; autopsy was refused.

Phenotypic variability

Intrafamilial variability was assessed in the 16 sibships with two or three affected sibs. The maximal intrafamilial difference was 3.6 SD in relative birth length (6.0 cm between a male and a female), 3.2 SD in childhood relative height and 3.4 SD in adult relative height (18.2 cm between two females). Hair hypoplasia also varied considerably (Fig. 2); in one sibship one affected child had normal and the other, severely hypoplastic hair (Table 1). Patients with most severe cases of growth failure were more likely to have recurrent infections, lymphocytopenia, severe childhood anaemia and Hirschsprung disease (Tables 1, 5).

Discussion

On the basis of the present study of 108 Finnish patients CHH seems to be clinically identical among the Amish and the Finns. Variation in severity is large in both ethnic groups; adult heights varied from 107 to 147 cm among the Amish patients [22] and from 103.7 cm to 149.0 cm among the Finnish patients [17]. In addition, a male patient in the present series measured 151.7 cm at the age of 15 years. Intrasibship variability can be considered a minimum measure of the degree of variability within a single disorder [10]. In CHH the intrasibship variability was considerable in all aspects; the maximal difference in relative height was 3.6 SD, and hair varied from normal to severely hypoplastic. Such wide phenotypic variability is unusual for an autosomal recessive disorder, but has been observed in some others [10, 21, 37]. In diastrophic dysplasia, another recessive chondrodysplasia, the maximal difference in relative height among 17 sibships was 1.6 SD [10].

Savage [34] described a pair of siblings with metaphyseal dysplasia, hypoplastic hair, normal immunity and proportionate dwarfism. This was presented as a variant form of CHH, since both the standing and the sitting heights were below the 3rd percentile. CHH affects growth in both the limbs and the spine, usually more severely in the limbs [17]. The present series included four patients with proportionate short stature. One of them had two sibs with disproportionate CHH. Therefore, normal sitting height-% does not rule out CHH.

Verloes et al. [38] described six patients with clinical and radiological features of CHH but no apparent clinical hypotrichosis. The hair shaft diameter was decreased in one patient. These patients were suggested to represent a variant form, perhaps allelic, of CHH. Rather than a variant form of CHH, our experience indicates that they lie within the spectrum of clinical variability for this condition.

That cell-mediated immunodeficiency is part of CHH has been well documented in the Amish [28, 36] and Finnish [29, 39] patients. Impaired in vitro cellular immunity was observed in 88% and increased susceptibility to infections in 56% of our patients. The degree of in vitro immunodeficiency, determined as in vitro responsiveness of lymphocytes to PHA, did not correlate with the severity of infectious problems; even marked T-cell deficiency was not always associated with infections. Pierce et al. reported normal or supranormal levels of spontaneous natural killer cell activity in CHH patients [25, 26] and suggested spontaneous natural cytotoxicity to be of major importance in these patients [24]. The incidence of malignancies is increased as observed in our series and others [7, 8, 31]. Francomano et al. [6] reported an incidence of 10% of malignancies in 113 Amish CHH patients: lymphoma in 3 patients, leukaemia in 2, skin neoplasms in 5, ocular cancer in 1 and bile duct carcinoma in 1 patient. In our series the incidence was 6%.

Administration of live viral vaccines to immunodeficient patients may have disastrous consequences [2, 23, 30]. In the literature we found four reports of complications in CHH patients: progressive vaccinia after smallpox vaccination in two patients [9, 24], fatal paralytic poliomyelitis after poliovirus vaccination (Sabin type) in one patient [33] and prolonged infection with poliovirus following oral poliovirus vaccination in one patient [41]. Live viral vaccines had been administered to most of the Finnish CHH patients without complications. However, since complications may be fatal, live viral vaccines should not be administered to CHH patients if clinical and in vitro studies suggest impaired cellular immunity.

Childhood anaemia has only recently been recognised as a part of CHH [18]. The red cells tend to be macrocytic even in patients with normal Hb [18]. The present study revealed severe childhood anaemia in 14 (16%) patients; tendency towards spontaneous recovery was great even in these cases.

Among the 77 Amish CHH patients two children had had aganglionic megacolon (Hirschsprung disease) [22]. Several CHH patients with Hirschsprung disease have been reported thereafter [1, 5, 7, 13, 14, 28, 32, 40]. Our series included eight patients with aganglionic megacolon. This experience definitely proves increased prevalence of aganglionic megacolon among CHH patients.

One Amish child with CHH had died of "coeliac syndrome", and a disorder of intestinal absorption was suspected in five others [11] who showed diarrhoea and failure to thrive in the first 2 years of life [22]. Irwin [11] described a child with CHH, occasional diarrhoea and gastro-intestinal symptoms suggestive of malabsorption. Of the Finnish patients, two had had symptoms suggesting malabsorption; gastro-intestinal infection was confirmed in both of them. Wood et al. [41] reported a CHH patient with severe T-cell deficiency, persistent diarrhoea and malabsorption following acute gastroenteritis. Electron microscope examination of faeces revealed excretion of rotavirus for more than 450 days with concurrent astrovirus infection for at least 225 days [41]. Another patient was studied at the age of 10 years because of lifelong symptoms of malabsorption; jejunal biopsy revealed extensive infestation with *Giardia lamblia*, no other cause of malabsorption was found [15]. Some CHH patients with suspected malabsorption probably have chronic gastro-intestinal infection.

Our conclusion is that the Amish and Finnish CHH patients share identical clinical features with wide range of variability in the degree of growth failure, immune deficiency, haematological disturbances and intestinal manifestations. Thus, parents of an affected child should be informed not only of the recurrence risk of CHH in future pregnancies but also of variability in expression.

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