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Extended Follow-Up of the Finnish Cartilage-Hair Hypoplasia Cohort Confirms High Incidence of Non-Hodgkin Lymphoma and Basal Cell Carcinoma

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Cartilage-hair hypoplasia (CHH) is an autosomal recessive chondrodysplasia with short stature, sparse hair and defective cell-mediated immunity. It is caused by mutations in the *RMRP* (ribonuclease mitochondrial RNA processing) gene, encoding the RNA component of the ribonuclease complex RNase MRP. The aim of this study was to further elucidate the risk and spectrum of cancer in CHH. A cohort of 123 Finnish patients with CHH (51 males) was followed for malignancy through the Finnish Cancer Registry. The number of identified cancers was compared with expected numbers of cancer using population-based data to obtain standardized incidence ratios (SIR). Hospital records were reviewed for clinical data related to the malignancies. During the follow-up (2,365 person-years; mean 19.2 years), 14 cases of cancer were diagnosed in the CHH cohort (expected number 2.0; SIR 7.0, CI 3.8–12). Non-Hodgkin lymphoma was the most frequent cancer type (n = 9; SIR 90.2, CI 39.0–180) followed by squamous cell carcinoma (3), leukemia (1) and Hodgkin lymphoma (1). One tumor was not histologically classified. Nine of the 14 cancers were diagnosed in patients less than 45 years of age. In addition, ten patients had basal cell carcinoma of the skin (expected number 0.3; SIR 33.2, CI 16–61). Patients with CHH have significantly increased risk for developing non-Hodgkin lymphoma or basal cell carcinoma at early age; the overall prognosis is poor. The underlying pathogenetic mechanisms remain to be elucidated in future studies. Careful follow-up, extending beyond pediatric age, is warranted for early diagnosis of malignancies. © 2008 Wiley-Liss, Inc.

Key words: chondrodysplasia; malignancy; *RMRP*; non-Hodgkin lymphoma; basal cell carcinoma

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INTRODUCTION

Cartilage-hair hypoplasia (CHH; OMIM 250250) is an autosomal recessive metaphyseal chondrodysplasia characterized by severe short-limbed short stature (adult height 110–140 cm) and sparse hair [McKusick et al., 1965; Mäkitie and Kaitila, 1993]. Other characteristics include defective erythropoiesis [Mäkitie et al., 1992] and increased incidence of Hirschprung disease [Mäkitie and Kaitila, 1993]. Defective immunity is an integral feature of CHH and usually involves only cellular but occasionally both cellular and humoral components. One-third of the patients have lymphopenia and over 80% show impaired lymphocyte proliferative responses to mitogen stimulation [Ranki et al., 1978; Mäkitie et al., 1998]. CD4+ cell counts and CD4+/CD8+ cell

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ratios are often subnormal [Mäkitie et al., 1998]. The abnormality of humoral immunity is characterized by IgA and/or IgG subclass deficiency in more than one third of the patients [Mäkitie et al., 2000]. CHH is particularly prevalent among the Finns, with >150 recognized patients in a population of 5.2 million and a carrier frequency of 1:76 [Mäkitie, 1992]. CHH is caused by mutations in the ribonuclease mitochondrial RNA processing (*RMRP*) gene, which encodes the RNA component of the ribonuclease complex RNase MRP [Ridanpää et al., 2001, 2003].

Patients with CHH have significantly increased mortality rate as compared with their parents and non-affected siblings [Mäkitie et al., 2001]. While defective immunity and infections predispose younger children to premature death, malignancies predominate as the cause of death in the older age groups [Mäkitie et al., 2001]. We have previously shown a sevenfold cancer risk, as compared with the age-adjusted expected incidence, in Finnish CHH patients evaluated between 1967 and 1995 [Mäkitie et al., 1999]. We have now re-evaluated the risk, spectrum and prognosis of malignancies associated with CHH by following a cohort of 123 Finnish patients with CHH through the Finnish Cancer Registry.

METHODS

The study comprised patients with CHH identified through two thorough epidemiologic surveys carried out in Finland in 1974 [Kaitila and Perheentupa, 1980] and in 1986 [Mäkitie, 1992], and patient records in the clinical database who were diagnosed between 1986 and 1995. The study was approved by the Ethics Review Board, Helsinki University Hospital. The diagnosis of CHH was based on clinical, radiographic, and genetic features [McKusick et al., 1965; Mäkitie and Kaitila, 1993]. In 92 patients the diagnosis of CHH was also confirmed by mutational analysis of *RMRP*, as previously described [Ridanpää et al., 2001].

The cohort was compared with the data in the Population Register Center of Finland. The correct personal identification number (ID) and vital status were attained for every cohort member. The parents and non-affected siblings were also traced through the Population Registry. Since January 1, 1967, all residents of Finland have had a unique personal ID, which is used in all official registries in Finland. The personal ID was used as the key when searching the CHH patients from the Finnish Cancer Registry.

The Finnish Cancer Registry is population-based and covers all of Finland since its foundation in 1952. Data is gathered from all hospitals, health centers, pathologic and hematologic laboratories, forensic autopsies and death certificates. The coverage is almost complete (99%) [Teppo et al., 1994] since the reporting is obligatory. All cancers are registered according to ICD-7 codes for the primary site.

The follow-up for the probands started from the date of the epidemiological survey through which they had been ascertained, and from the date of diagnosis for all the affected siblings found through family search and for patients diagnosed after 1986. The follow-up for the parents started from the birth of the index patient with CHH and for the siblings from their date of birth. If these dates were before 1967, the follow-up was started from January 1, 1967. The follow-up of all the patients, siblings and parents ended at death or on December 31, 2004.

The number of cases and person-years at risk were calculated by five-year age groups separately for four calendar periods (1967–1976, 1977–1986, 1987–1995, 1996–2004). The expected numbers of cases for total cancer and for specific cancer types were calculated by multiplying the number of person-years in each age-group by the corresponding average cancer incidence in the entire Finnish population during the observation period. The age-group specific numbers were then summed over periods, and genders were combined into broader age categories (15-year bands and all ages). The observed number of cases was divided by the expected number to obtain standardized incidence ratio (SIR). The exact 95% confidence intervals are given on the presumption that the number of observed cases followed a Poisson distribution. Due to usually non-aggressive clinical course, basal cell carcinomas were not included in the calculation of the overall cancer risk but are presented separately. Data on clinical, genetic and immunological features and disease outcome were collected from hospital records for the CHH patients with malignancy. Kaplan–Meier survival method was used to estimate cancer-free survival.

RESULTS

The CHH group comprised 123 patients (51 males) (index patients and affected siblings combined); their age distribution is presented in the Table I. The mean length of follow-up was 19.2 years and was in total 2,365 person-years. During the follow-up 14 cases of cancer (excluding basal cell carcinomas)

TABLE I. Age Distribution of the 123 Finnish Patients With Cartilage-Hair Hypoplasia

Age group (years)	Number of patients			Person-years
	Females	Males	All	
0–14	52	41	93	812.5
15–29	8	8	16	840.4
30–44	7	1	8	489.6
45–59	5	1	6	192.3
60–74			—	31.1

were diagnosed, while the expected number was 2.0 (SIR 7.0, CI 3.8–12) (Tables II and III). Non-Hodgkin lymphoma was the most frequent cancer diagnosis (n = 9). The SIR for non-Hodgkin lymphoma was 90.2 (CI 39–180). Three patients had squamous cell carcinoma, and chronic lymphatic leukemia and Hodgkin lymphoma were diagnosed in one patient each (Table III). In addition to the above, 10 patients had basal cell carcinoma of the skin, compared with 0.3 expected (SIR 33.2, CI 16–61).

Two patients had multiple malignancies: the other has had a non-Hodgkin lymphoma and lymphomatoid papulosis, both with multiple recurrences, and the other had squamous cell carcinoma in the finger and was diagnosed 18 months later with undifferentiated lung carcinoma.

The majority of the cancers, 9/14 (64%), were diagnosed in young adults of 15–44 years (Table III). In the age range of 15–29 years, the SIR for non-Hodgkin lymphoma was 130 (16–480). The Kaplan–Meier estimate of probability of cancer-free survival by the age of 65 is 0.59 meaning that 41% of the CHH patients will have a cancer diagnosis by that age (Fig. 1). The risk of basal cell carcinoma was also increased at young age: at 15–29 years the SIR was 62 (CI 1.6–340). The cancers were equally distributed in females and males. The cancers were associated with poor prognosis: the underlying cancer was the cause of the death in nine patients and the median survival time after the cancer diagnosis was 3 months (range 1–30 months).

Disease-causing *RMRP* mutations had been identified in 9 of the 14 patients with malignancy. All were homozygous (six) or heterozygous (three) for the major mutation 70A > G (Table III). Seven out of the 14 malignancies were of B-cell origin. Immunological data collected from the hospital records showed that serum IgG levels had been high in several patients tested prior to the cancer diagnosis (Table III). As indicated by the phytohemagglutinin stimulation test, all patients tested had impaired T-cell function (Table III). None of the patients with cancer had received stem cell transplantation.

The cohort of unaffected siblings consisted of 159 persons with a total follow-up of 4,779 person-years and mean follow-up of 30.0 years. Most of the siblings (119/159; 75%) were less than 15 years old. During the follow-up nine cancers were diagnosed, while the expected number was 5.9 (SIR 1.5, CI 0.7–2.9); no cases of lymphoma were observed. Basal cell carcinoma of the skin was diagnosed in two siblings versus 1.0 expected (SIR 1.9, CI 0.2–6.9).

The cohort of 196 parents had a mean follow-up time of 24.9 years (4,879 person years). The overall cancer risk of the parents did not differ from the general population (21 observed cancers vs. 21.5 expected; SIR 1.0, CI 0.6–1.5). The number of basal cell carcinomas among the parents was two compared with 4.2 expected.

DISCUSSION

The present study shows a sevenfold increased overall cancer rate in patients with CHH, as compared with the normal population. Non-Hodgkin lymphomas and basal cell carcinoma were the most prevalent types of cancer, with SIRs of 90 and 33, respectively. The findings are similar to our previous observations [Mäkitie et al., 1999] and also with reports by others [Roberts and Arnold, 1984; Van Der Burgt et al., 1991; Gorlin, 1992; Bonafe et al., 2005].

With the 10-year extension of follow-up of the CHH cohort since the previous study, the total number of reported cancers has increased from 5 to

TABLE II. Observed and Expected Numbers of Cancers and Standardized Incidence Ratios (SIR) With Their 95% Confidence Intervals (CI) in 123 Finnish Patients With CHH From 1967 to 2004

Cancer type/age group	Observed	Expected	SIR	95% CI	*P*
All cancers*	14	2.0	7.0	3.8–12	<0.001
0–14 years	1	0.12	8.5	0.2–47	
15–29 years	4	0.24	17	4.6–44	<0.001
30–44 years	5	0.50	10	3.3–24	<0.001
45–59 years	3	0.85	3.5	0.7–10	
60–74 years	1	0.31	3.2	0.1–18	
Non-Hodgkin lymphoma	9	0.09	90	39.0–180	<0.001
0–14 years	1	0.01	130	3.23–710	<0.05
15–29 years	3	0.02	130	16–480	<0.001
30–44 years	3	0.02	120	25.2–360	<0.001
45–59 years	2	0.03	67	8.1–240	<0.001
60–74 years	—	0.01	—	0–330	
Basal cell carcinoma	10	0.30	33	16–61	<0.001
0–14 years	—	0	0	0–3,000	
15–29 years	1	0.02	62	1.6–340	<0.05
30–44 years	4	0.08	51	14–130	<0.001
45–59 years	3	0.14	21	4.3–61	<0.001
60–74 years	2	0.06	32	3.8–120	<0.01

*Basal cell carcinomas not included.

TABLE III. Clinical Characteristics of the 14 Cartilage-Hair Hypoplasia Patients and Malignancy

	Malignancy						Immunology			
Sex/age	Type	Primary location	Stage	Outcome	Survival	Mutation	IgG (g/L)	IgA (g/L)	IgM (g/L)	PHA (%)
M/40	Non-Hodgkin lymphoma (B)	Abdominal	IVB	Deceased	0 months	70A > G/262G > T	13.0	0.76	0.50	**10**
F/45	Non-Hodgkin lymphoma (B)	Mediastinal	IVB	Deceased	3 months	Not tested	12.6	1.06	0.68	**11**
F/46	Non-Hodgkin lymphoma (B)	Intestine	IVB	Deceased	6 months	70A > G/70A > G				
F/22	Non-Hodgkin lymphoma (NA)	Intestine	IVB	Deceased	2 months	Not tested	24.8	1.82	0.56	**19**
F/6	Non-Hodgkin lymphoma (B)	Adrenal	IVB	Deceased	9 months	dupTACTCTGTGA at 13/70A > G	15.2	0.9	0.7	**32**
M/20	Hodgkin lymphoma	Mediastinal	IIIB	Deceased	1 month	70A > G/70A > G	32	2.47	3.15	**25**
M/21	Non-Hodgkin lymphoma (NA)	Mediastinal	I	Deceased	1 month	70A > G/70A > G		—	—	**10**
F/38	Chronic lymphatic leukemia (B)	Bone marrow	—	Deceased	30 months	70A > G/262G > T	14.6	**0.42**	0.78	**24**
F/62	Squamous-cell carcinoma Undifferentiated carcinoma	Skin Lung	I NA	Deceased	18 months	not tested		—	—	—
M/26	Non-Hodgkin lymphoma	Ventricle	NA	Alive	FU 4.5 years	70A > G/70A > G	13	1.43	1.23	**34**
M/32	Non-Hodgkin lymphoma (T) Lymphomatoid papulosis	Cervical Skin	IA (relapsed) multiple relapses	Alive	FU 11 years	Not tested	10.7	0,91	0,83	**22**
F/33	Non-Hodgkin lymphoma (B)	Abdominal	IVA	Alive	FU 4.5 years	Not tested	14.5	**0.42**	0.78	**37**
F/40	Squamous-cell carcinoma	Vocal cord	I	Alive	FU 13 years	70A > G/70A > G	—	—	—	**29**
F/45	Squamous-cell carcinoma	Skin	NA	Alive	FU 6 years	70A > G/70A > G	—	—	—	—

B, B-cell origin; T, T-cell origin; FU, follow-up; NA, not assessed; Ig, immunoglobulin; PHA, phytohemagglutinin stimulation test. Immunoglobulin levels were compared with age-specific reference values. For PHA, response of <50% of normal was considered subnormal. Subnormal values are in bold and high values are underlined.

FIG. 1. Kaplan–Meier estimate of cancer events in patients with Cartilage-hair hypoplasia. The estimate is based on a cohort of 123 Finnish patients with CHH, followed for 39 years, and gives a probability of a cancer event (excluding basal cell carcinoma) of 41% by the age of 65 years. The length of follow-up for each subject is indicated.

14 and the number of non-Hodgkin lymphomas from 3 to 9. The number of basal cell carcinomas has tripled [Mäkitie et al., 1999]. With the extended follow-up of the Finnish CHH cohort it has become evident that the cancer diagnoses are made at relatively young age and that the prognosis is in general poor. Up to 64% of the patients with cancer were between 15 and 45 years of age at diagnosis. The SIR for non-Hodgkin lymphoma was as high as 132 at the 15–29 year age range. Most of the malignancies resulted in premature death; the median survival time after the diagnosis was only three months. Patients with CHH may be susceptible to multiple cancers or to cancer at multiple sites, as seen in two of our patients and as reported by others [Torkzad et al., 2002; Eisner and Russell, 2006].

Both cell-mediated [Mäkitie et al., 1998] and humoral immunity [Ranki et al., 1978] may be affected in CHH. This reflects into the pattern of cancers. The vast majority of the malignancies were non-Hodgkin lymphomas. In addition, basal cell carcinomas were over-represented. Overall, patients with primary immunodeficiency syndromes have almost 10,000 times higher risk for developing cancer than age-matched controls [Mueller and Pizzo, 1995; Paller, 2005]. After infections, especially pneumonia and bacteremia [Chang et al., 2006], malignancy is the second leading cause of death in subjects with congenital immunodeficiency disorders [Mueller and Pizzo, 1995]; non-Hodgkin lymphoma and skin cancers are the most common cancers [Paller, 2005]. In general, the incidence of lymphoproliferative disorders in immunodeficiency patients ranges up to 15% in ataxia telangiectasia and

Wiscott–Aldrich syndrome [Oertel and Riess, 2002; Paller, 2005]. Our observations of 90- and 33-fold increased risk of non-Hodgkin lymphoma and skin cancers, respectively, in patients with CHH are parallel to observations in other immunodeficiency syndromes.

The pathogenesis leading to a lymphoproliferative process in primary immunodeficiences is related to the underlying disease. Defective DNA repair [Eyfjord and Bodvarsdottir, 2005] and deficiency of the FAS apoptosis pathway [Ramenghi et al., 2000] contribute to the development of neoplasms in ataxia telangiectasia and autoimmune lymphoproliferative syndrome, respectively. However, proliferation of Ebstein-Barr virus (EBV) positive B-cells in the absence of effective immune surveillance is the factor involved in the pathogenesis of majority of immunodeficiency-associated lymphoid proliferations [Okano, 2001]. EBV-specific cytotoxic T-lymphocytes are considered to be the most important defense against EBV infection [Okano, 2001]. Consequently, patients with immune deficiencies affecting T-cell function, or the T-cell/B-cell interaction, as is also the case in CHH, are the most susceptible to uncontrolled EBV-induced B-cell proliferation [Okano, 2001]. The degree of the individual immune deficiency reflects the clinical picture of the EBV-associated lymphoproliferation. The only manifestation of lymphoproliferation may be monoclonal gammopathy [Cotelingam et al., 1985] or self-limited clonal expansion of a B-cell population [Laszewski et al., 1990], as described in patients with Wiscott–Aldrich or variable immunodeficiency syndromes, respectively. In contrast, in X-linked lymphoproliferative disease the outcome is poor [Okano, 2001]. A re-evaluation of the serum IgG levels measured in our earlier study [Mäkitie et al., 1998] reveals that the CHH patients with lymphoid malignancy had high IgG levels several years before the diagnosis of their malignancy (Table III). Further studies are needed to evaluate whether B-cell lymphomas in CHH are another manifestation of a virus-related lymphoproliferation in immunodeficient patients.

The mechanism by which the *RMRP* mutations in CHH predispose to both lymphoid and epithelial malignancies is unknown. The *RMRP* mutations disturb ribosomal processing by altering the ratio of the short versus long form of the 5.8S rRNA in yeast [Hermanns et al., 2005]. Recent data suggest that defective ribosomal processing in CHH is associated with altered cytokine signaling and upregulation of genes involved in cell cycle and cell growth control in terminally differentiating cells in lymphocytic and chondrocytic cell lines [Hermanns et al., 2005]. It can be speculated that upregulation of some of these genes, including *IL8* and *G0S2*, may be involved in the pathogenesis of malignancies in CHH [Hermanns et al., 2005]. The level and type of functional impairment may contribute to the severity of short stature or predisposition to cancer [Thiel et al., 2005].

Allogeneic stem cell transplantation (SCT) is an established therapeutic approach in the treatment of severe immunodeficiency syndromes [Antoine et al., 2003]. Clinically severe immunodeficiency has been the indication of SCT in four CHH patients [Berthet et al., 1996; Guggenheim et al., 2006]. All of them were donor chimeras several years after transplantation; one needed a second transplant [Guggenheim et al., 2006]. The immune reconstitution has been successful in all of them. The course of chondrodysplasia has been unaffected, even though the SCT has been performed at young age [Berthet et al., 1996]. Consequently, SCT seems to be a feasible and valuable therapeutic option for CHH patients with recurrent infections and severe immunodeficiency. It is obvious that SCT will not resolve the problem of other malignancies than those involving the hematopoietic system. However, due to increased risk of non-Hodgkin lymphomas, any CHH patient with severe immune deficiency should be considered for SCT.

The cancer incidence of the carriers of the CHH gene mutation, that is, the parents, was not different from the normal population. The incidence of cancer among the siblings was a little higher than in the general Finnish population, but the difference was not statistically significant. These findings are similar to our previous observations and confirm that heterozygous carriers of *RMRP* mutations are not at increased risk for malignancies.

In conclusion, CHH patients have a substantially high risk of non-Hodgkin lymphoma and basal cell carcinoma at young age. Immunodeficiency is likely to play a central role in the pathogenesis of the malignancies in CHH patients. Allogeneic stem cell transplantation may be a therapeutic option for selected CHH patients with immunodeficiency. Further studies are needed to elucidate the pathogenetic mechanisms leading to the development of malignancies. Careful follow-up, extending beyond pediatric age, is warranted for early diagnosis of malignancies.

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