

## CLINICAL STUDY

# Congenital IGF1 deficiency tends to confer protection against post-natal development of malignancies

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## Abstract

**Objective:** To investigate whether congenital IGF1 deficiency confers protection against development of malignancies, by comparing the prevalence of malignancies in patients with congenital (secondary) deficiency of IGF1 with the prevalence of cancer in their family members.

**Method:** Only patients with an ascertained diagnosis of either Laron syndrome (LS), congenital IGHD, congenital multiple pituitary hormone deficiency (cMPHD) including GH or GHRHR defect were included in this study. In addition to our own patients, we performed a worldwide survey and collected data on a total of 538 patients, 752 of their first-degree family members, of which 274 were siblings and 131 were further family members.

**Results:** We found that none of the 230 LS patients developed cancer and that only 1 out of 116 patients with congenital IGHD, also suffering from xeroderma pigmentosum, had a malignancy. Out of 79 patients with GHRHR defects and out of 113 patients with congenital MPHD, we found three patients with cancer in each group.

Among the first-degree family members (most heterozygotes) of LS, IGHD and MPHD, we found 30 cases of cancer and 1 suspected. In addition, 31 malignancies were reported among 131 further relatives.

**Conclusions:** Our findings bear heavily on the relationship between GH/IGF1 and cancer. Homozygous patients with congenital IGF1 deficiency and insensitivity to GH such as LS seem protected from future cancer development, even if treated by IGF1. Patients with congenital IGHD also seem protected.

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## Introduction

Linked to their proliferative, differentiation and apoptotic properties, both GH and insulin-like growth factor 1 (IGF1) have been identified as risk factors for certain malignancies (1–5), even in the pediatric age group and young adults (6–8). There is also evidence that most tumors and transformed cells display increased IGF1 receptor (IGF-1R) concentration and high *IGF1R* mRNA, causing enhanced IGF1 binding (9, 10), leading to the axiom that overexpression of IGF1R is a pre-requirement for acquisition or progress of malignant tumors (11). Further evidence for the link between GH, IGF1 and cancer is the successful use of GH and IGF-1R-blocking agents in the treatment of malignancy (12). The above findings led us to investigate the reverse situation, namely whether congenital defects of GH and IGF1 action would diminish or prevent the development of cancer.

In 2007, we reported preliminary data on 169 patients with Laron syndrome (LS) and on 250 of their first- and second-degree relatives and found that none of the homozygous LS patients had developed cancer,

whereas 24% of their heterozygous family members had (13). We also showed that 35 patients with congenital (c) IGHD and 18 with GHRH receptor (R) mutation reported no malignancies. In contradiction, 9–24% of their family members had a history of cancer.

The aim of the present study was to extend our findings by enlarging the number of patients with LS and cIGHD and to collect data on patients with GHRHR mutations and congenital multiple pituitary hormone deficiency (cMPHD), including GH.

## Methods

This retrospective study was approved by the ethics committee. The following procedures were employed to collect the data:

- We updated data from our medical charts of LS patients, which had increased to 67 and, 28 patients were with cIGHD.
- Sent questionnaires to authors of published reports on patients with the diagnoses mentioned.

c. Approached personally the physicians from countries we knew there are patients with the above diseases.

Out of the several hundreds of questionnaires sent, we received replies from over 80 colleagues. The limitations found in collecting the data were:

- i. Some of the authors reporting the patients had performed only the genetic analysis and had no clinical information on the patients.
- ii. Many of the patients live in small villages and countries inaccessible to the treatment, so patient follow-up was lost. Prevalence of cancer types could also not be obtained from these countries.
- iii. Lack of cooperation.

### Statistical analysis

The collected data were analysed using the BMDP statistical software (14). One-way and two-way ANOVA were used to analyse continuous variables (age) and as for discrete variables (diagnosis/type of malignancy),  $\chi^2$  test and Fisher's Exact test were used. A *P* value <0.05 was considered statistically significant.

### Subjects

We were able to collect data on a total of 538 patients, 752 of their first-degree family members (parents,

siblings and offspring) and 131 further family members. Only patients with the following ascertained diagnoses were included in this study:

- i. LS – secondary congenital deficiency of IGF1 and primary GH insensitivity, due to defects in the GH receptor.
- ii. Primary congenital isolated hGH deficiency (cIGHD).
- iii. GHRHR receptor (R) defect – secondary hGH deficiency.
- iv. Congenital multiple pituitary hormone deficiency, including hGH (cMPHD).

A high percentage of the LS, cIGHD and GHRHR patients underwent genetic molecular analysis. In most of the cMPHD patients, the diagnosis was based on clinical and endocrine evaluation. Unfortunately, the ages were not stated for all patients and relatives, nor was the age of diagnosis of malignancies stated in all questionnaires.

### Results

Table 1 shows the number and age distribution of patients as well as that of the first-degree relatives, including siblings and further relatives in each diagnostic group. It is of note that we were able to collect data on half or more of the presumed total number of LS patients (not including the Ecuadorian

**Table 1** Number and age of the patients and their relatives in four diagnostic groups with secondary congenital IGF1 deficiency.

	Diagnostic groups				Total
	Laron syndrome (GHR defects)	cIGHD	GHRHR defect	cMPHD	
<b>Patients</b>					
Total number ( <i>n</i> )	230	116	79	113	538
Number with known age	166 <sup>a</sup>	106 <sup>b</sup>	16 <sup>c</sup>	113 <sup>d</sup>	401 <sup>e</sup>
Age range	1–75	1.5–55	2.8–88	0.25–87	0.25–87
Mean age $\pm$ s.d.	19.2 $\pm$ 15	18.3 $\pm$ 12.8	29.7 $\pm$ 23	29.4 $\pm$ 18.7	22.2 $\pm$ 16.7
<b>First-degree relatives</b>					
Total number ( <i>n</i> )	218	203	150	181	752
Number with known age	157	200	12	173	542
Age range	1–81	1–84	3–93	1–84	1–93
Mean age $\pm$ s.d.	37.7 $\pm$ 19.1	32.2 $\pm$ 19.1	48 $\pm$ 24	31.4 $\pm$ 18.5	33.8 $\pm$ 19.3
<b>Further relatives</b>					
Total number ( <i>n</i> )	113	13	4	1	131
Number with known age	38	12	4	–	–
Age range	29–85	28–83	26–59	–	26–85
Mean age $\pm$ s.d.	61 $\pm$ 14.7	61.83 $\pm$ 17.9	43.2 $\pm$ 17.1	–	59.8 $\pm$ 16
<b>Siblings only</b>					
Total number ( <i>n</i> )	86	96	6	86	274
Number with known age	65	95	6	83	249
Age range	1–80	1–81	3–47	1–56	1–81
Mean age $\pm$ s.d.	25.7 $\pm$ 17.3	22.2 $\pm$ 19	36.3 $\pm$ 16.6	19.2 $\pm$ 13.3	22.4 $\pm$ 17
<b><i>P</i> values</b>					
Patients versus first-degree relatives	<0.001	<0.001	0.03	0.37	<0.001
Patients versus siblings	0.001	0.08	0.49	<0.001	0.7

Number of patients above 30 years: <sup>a</sup>31; <sup>b</sup>19; <sup>c</sup>6; <sup>d</sup>51; <sup>e</sup>107.

**Table 2** The prevalence of malignancy in the four diagnostic groups.

	Diagnostic groups				Total
	Laron syndrome	cIGHD	GHRHR defects	cMPHD	
<b>Patients</b>					
Total number (n)	230	116	79	113	538
Number of malignancies	0	1 <sup>b</sup>	3 <sup>c</sup>	3 <sup>d</sup>	7
Prevalence of malignancy (%)	0.0	0.9	3.8	2.7	1.3
<b>First-degree relatives</b>					
Total number (n)	218	203	150	181	752
Number of malignancies	18 (15)	7 (6)	0	5+1 <sup>a</sup> (6)	30 (26+1) <sup>a</sup>
Prevalence of malignancy (%)	8.3	3.4	0.0	2.8	4.0
<b>Further relatives</b>					
Total number (n)	113	13	4	1	131
Number of malignancies	25 (24)	4 (4)	1 (1)	1 (1)	31 (30)
Prevalence of malignancy (%)	22.1	30.8	25	–	23.7
<b>Siblings only</b>					
Total number (n)	86	96	6	86	274
Number of malignancies	5 (4)	2 (2)	0	2 (2)	9 (80)
Prevalence of malignancy (%)	5.8	2.1	0.0	2.3	3.3
<b>P values</b>					
Patients versus first-degree relatives	<0.001	0.43	0.04	1	0.019
Patients versus further relatives	<0.001	<0.001	0.182	–	<0.001
Patients versus siblings	0.005	0.59	1	1	<0.165

Number in parentheses indicate number of individuals. <sup>a</sup>Indicates one suspected malignancy; <sup>b</sup>includes one male basal cell carcinoma diagnosed at 15 years; <sup>c</sup>includes one male Hodgkins lymphoma diagnosed at 43 years and two male skin cancers (one diagnosed at 37 years and the other unknown); <sup>d</sup>includes two female thyroid carcinoma diagnosed at 10.5 and 52 years and one male planocellular carcinoma of the nasal septum diagnosed at 66 years of age.

cohort) and probably a large percentage of those with GHRHR mutations.

In total, the patients were significantly younger than their first-degree relatives ( $P < 0.001$ ), though the differences in the GHRHR defect and the cMPHD groups were not significant. Also, there was no significant age difference when we compared the age of patients with that of their siblings. It is worth mentioning that the patients' age range was wide, reaching 85 years, and that 25% of the patients with recorded age were above 30 years of age.

Table 2 shows the prevalence of malignancies in the patients and their relatives in each diagnostic group. It is seen that none of the 230 LS patients had developed a malignancy, despite the fact that 66 had been or are still treated by IGF1 and two had received hGH as well. The difference between the prevalence of malignancies in all the first-degree relatives and that in the siblings alone, with that in the patients was significant ( $P < 0.001$ ,  $P = 0.005$ , respectively). Out of the 116 patients with cIGHD, only one boy suffers from xeroderma pigmentosum was reported to have a basal cell carcinoma (BCC) diagnosed at the age of 15 years. Fifty-nine of cIGHD patients had been treated with hGH, including the boy who developed BCC. Out of the 79 patients with GHRHR mutations (12 previously treated with hGH), three had cancer (one of them previously treated with hGH) and so had three out of 113 patients with cMPHD. In the latter group, 97 had been previously treated with hGH, in addition to other hormone replacement therapy, and among them, two had developed malignancies.

Out of 752 first-degree relatives, 26 reported 30 instances of cancer ( $P = 0.019$ ) and out of 131 further

relatives, 30 reported 31 instances of cancer ( $P < 0.001$ ). Nine malignancies were reported in eight of the siblings ( $P = 0.165$ ). In Table 3, it is evident that the majority are lung, breast and prostate cancer, followed by colon and gastric cancer.

## Discussion

In this attempt of a worldwide survey of the prevalence of cancer in patients with secondary congenital IGF1 deficiency, we confirmed and enlarged our preliminary observation that patients with LS, having both congenital GH and IGF1 deficiency and insensitivity to endogenous and exogenous GH, seem protected from the development of cancer (13). That observation was also confirmed by findings in the large Ecuadorian cohort of LS patients (15). Considering that the latter cohort accounts for 100 living patients, it is obvious that over 300 patients with LS, the majority now being adults, have not developed cancer.

In contradistinction, 15 of their 218 first-degree relatives in the present survey and 24 out of 131 further relatives (proven or supposed heterozygotes for the disease) reported 43 instances of cancer. The difference between presence or absence of malignancy between patients with LS and their first-degree relatives and siblings was statistically significant ( $P < 0.001$ ,  $P = 0.005$ , respectively). In the Ecuadorian cohort, 80 out of 1032 relatives died of cancer (15).

Only one boy out of 116 patients with congenital IGHG presented a BCC of the cheek. This patient also suffered from xeroderma pigmentosum, a genetic defect

**Table 3** Types of cancer reported in first and further-degree relatives of patients with congenital insulin-like growth factor 1 deficiency.

Type of cancer	Number (age at diagnosis in years)	Diagnosis of probands
Lung	9 (48–72)	7 LS, 1 IGHD, 1, MPHD
Breast	7 (45–75)	5 LS, 2 IGHD
Prostate	7 (48–76)	6 LS, 1 IGHD
Colon	6 (58–63)	3 LS, 3 IGHD
Gastric	6 (43, unk.)	4 LS, 1 IGHD, 1 MPHD
Leukemia	4 (3–84)	2 LS, 1 MPHD, 1 GHRHR defect
Unknown primary	4 (unk.)	3 LS, 1 IGHD
Pancreas	2 (54, 73)	1 LS, 1 MPHD
Uterus	2 (48, unk.)	2 LS
Bone	2 (17, unk.)	1 IGHD, 1 MPHD
Lymphoma	2 (62, unk.)	1 IGHD, 1 MPHD
Nose	1 (unk.)	1 LS
Renal	1 (unk.)	1 LS
Thyroid	1 (25)	1 LS
SCC	1 (65)	1 LS
Brain	2 (4, 56) + 1 susp. (13)	2 LS (susp. – MPHD)
Liver	1 (unk.)	1 LS
Esophagus	1 (unk.)	1 LS
Bladder	1 (81)	1 LS
Testis	1 (unk.)	1 LS
Total	61 malign. + 1 susp.	

UNK, unknown.

involving DNA repair. Out of the 79 patients with GHRHR mutation and 113 with congenital MPHD, six instances of cancer were reported, three with previous hGH treatment.

The lack of complete protection against cancer in the patients with GHRHR mutations and those with congenital MPHD could be due either to the fact that some patients still secrete small amounts of GH (16), that some are sensitive to the exogenously administered hGH treatment or other environmental noxae and/or belonging to a familial genetic trend for malignancy.

The fact that heterozygote family members, which secrete IGF1 and/or hGH, develop malignancies, in a relatively high incidence for the given ethnic groups, may favor the above assumption. It is also of note that the types of malignancies and their prevalence in our study group correspond to the prevalence in the overall population (17).

The difference in age range between the patients who did not develop cancer and the family members who developed cancer may be considered to influence our conclusions, although our own cohort of 67 LS and 28 cIGHD patients consists almost entirely of adult patients, pointing to the fact that age may be a confounding factor but not the major factor in the development of cancer. Comparing our data with the incidence of cancer in Israel and neighboring countries, it is evident that the incidence in the age group 0–19 years is 10% of that occurring in the age group 20–49 years. In these populations, breast cancer is diagnosed as early as 15 years (The web site of the Israeli National Cancer Registry, [www.health.gov.il/icr](http://www.health.gov.il/icr)).

The present reported clinical data is supported by recent animal experiments which prove that the homozygous GHR-KO-mouse (18, 19) exhibits statistically significant reductions in the overall incidence of malignancy (20–22). An earlier experimental study also revealed that dw/dw rats, congenitally deficient in GH, are resistant to dimethylbenzanthracene (DMBA)-induced mammary carcinoma (23).

It is of interest that animal experiments with cMPHD mice (Ames and Snell) have shown different degrees of protection against malignancies. While the Snell mice exhibit significant protection against the development of cancer (24), the Ames mice are not different from their litter mates regarding the prevalence of malignancies, but develop the cancer at an older age (25). This resembles our data in man and is possibly due to the secretion of small amounts of GH. Further support for our hypothesis that IGF deficiency tends to protect against cancer is the successful use in oncology of IGF1R-blocking drugs (12).

In conclusion, our findings bear heavily on the relationship between GH/IGF1 and cancer. Follow-up of the homozygous patients with congenital IGF1 deficiency and insensitivity to GH will show whether they are protected from future cancer development, even if treated with IGF1. Patients with congenital IGHD, nowadays treated with hGH in most countries, also seem protected (the only instance of cancer reported needs further clarification).

The secretion of small amounts of endogenous GH/IGF1 such as that shown in few patients with GHRHR mutation or with congenital MPHD, as well as their normal secretion in heterozygous carriers of LS or IGHD gene defects, may play a role in the development of cancer in these patients.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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