Health and Lifestyle of Adult Patients with Congenital Isolated Growth Hormone Deficiency Treated in Childhood

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ABSTRACT: **Background:** Treatment of patients with childhood growth hormone deficiency is usually terminated at the end of puberty. Follow-up into adult age is rare, even more so in patients with congenital isolated growth hormone deficiency (cIGHD).

Objectives: To assess the clinical and social characteristics of adults with cIGHD who received growth hormone (hGH) treatment in childhood.

Methods: Thirty-nine patients (23 men, 16 women) diagnosed in our clinic with cIGHD at 7 ± 4.2 years, and treated with hGH during childhood for 2–18 years, were followed into adulthood (mean age 30.7 ± 13.3 years). Ascertained detailed data were found for 32 patients.

Results: Mean ± SD height for males was 160.2 ± 10.6 cm and for females 146.4 ± 5.4 cm. All patients achieved full sexual development and 14 were married. After cessation of GH treatment and with advanced age all exhibited a progressive increase in adiposity to the degree of obesity. Twelve patients suffered from hyperlipidemia, 4 developed diabetes mellitus, and 5 have cardiovascular diseases. One patient died in an accident. None developed cancer. Of the 39 patients, 22 have an education level of high school or higher, and 2 are in special institutions. Most are employed in manual labor.

Conclusions: Patients with congenital IGHD who do not receive early and regular replacement treatment are prone to lag in achieving normal height and suffer from educational and vocational handicaps.

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KEY WORDS: congenital isolated growth hormone deficiency (IGHD), growth hormone releasing hormone receptor (GHRH-R) mutations, *hGH-1A* gene deletion, hGH treatment, adult GHD, educational and occupational outcomes

Isolated growth hormone deficiency (IGHD) can be congenital (c) or acquired [1]. The incidence of cIGHD varies within different populations and ethnic groups, being more prevalent in populations with consanguineous marriages. It is familial in approximately 30% of patients, demonstrating a genetic origin [2]. Its etiology may be either mutations in the growth hormone releasing hormone receptor (*GHRH-R*) gene or deletions in the *hGH-1A* gene [3-8], the latter occurring more frequently. Both types are of recessive heredity.

Our clinic has diagnosed a large cohort of patients with cIGHD who were diagnosed in childhood, and reported their physical growth and development before and during human growth hormone (hGH) treatment until the end of puberty [9]. We describe here the clinical, educational, vocational and social outcomes of the patients followed into adult age without further hGH treatment.

SUBJECTS AND METHODS

The study is retrospective. The data were extracted from medical records in our clinic, and from outside medical clinics where these patients were followed via telephone conversations with them and/or their physicians. In addition, we used the National Diabetes Register of the Ministry of Health and the Mortality Register of the Ministry of Interior to crosscheck for diabetes and mortality. This is possible in Israel as every newborn receives an ID number.

Genetic analysis was performed using restriction endonuclease analysis of DNA fragments, either in our laboratory or by Dr. John Parks in Atlanta, GA, USA. The GHRH-receptors mutation was diagnosed by analyzing the 13 coding exons and intron-exon boundaries; the proximal promoter of the GHRH-R was performed by denaturing gradient gel electrophoresis [10].

The diagnosis of isolated GH deficiency in the patients was ascertained by at least two stimulations and/or familial incidence. Deficiency of other pituitary hormones was excluded in all patients by specific tests. Height was measured with a Harpenden Stadiometer. Subscapular skinfold thickness was measured with a Harpenden caliper. Subcutaneous skinfold centiles for gender and age were taken from McDowell et al. [11]. Body mass index (BMI) was calculated by the formula weight/height^2. Stretched penile length was measured with a caliper using the norms of Hatipoğlu and Kurtoğlu [12] and testicular volume with the Prader orchidometer [23], then related to the norms of Zilka and Laron [13]. Serum insulin growth factor-1 (IGF-I) concentration was measured by radioimmune assays. IGF-1 SDS was calculated according to Bidlingmaier

*This study fulfills part of the requirements for the MD degree of Efrat Ben-Nun Yaari at the Sackler Faculty of Medicine, Tel Aviv University

et al. [14]. The study was approved by the Hospital Ethics Committee.

STATISTICAL ANALYSIS

The data were analyzed using BMDP software. Data are expressed as means ± standard deviations. Analysis of variance (ANOVA) was used to compare continuous variables. Since the sample size was relatively small, we looked for correlations between continuous variables using Spearman's correlation. A *P* value of ≤ 0.05 was considered significant.

RESULTS

The cohort of patients with cIGHD in our clinic consisted of 39 patients (23 men and 16 women, mean age 30.7 ± 13.3 years) who were referred during the period 1958–1992 and diagnosed as homozygous for a *hGH-1A* gene deletion (n=32) or a *GHRH-R* mutation (n=7). Eighteen patients belonged to consanguineous families, 15 of them to 6 families. All had a history of typical signs and symptoms of GHD since birth and had received hGH treatment in their childhood at a daily dose of 30–35 μg/kg/day. The duration of treatment ranged between 2 and 18 years. No patients were resistant to GH treatment and no antibodies against hGH were found [15].

The absence of the 3.8 Kb "Bam HI" fragments that contain the *hGH-1* gene was found in four families [10]. All other family members were heterozygotes for the mutation, which represents fragments of either 4.5 or 6.7 kb of the *hGH-1* gene. A GHRH-R missense mutation in exon 11 (R357C) was found in seven patients from two Israeli Arab families [10].

Of 39 cIGHD patients, reliable data were available for 32. The data could not be obtained for seven patients due to change of address and/or insurance company, or neglect to attend follow-up visits, and thus they were excluded.

The diagnosis of isolated GH deficiency was verified by very low or undetectable levels of IGF-I. The demographic, genetic and main clinical results are presented in Table 1, as determined on their last visit to our clinic.

It is evident that 27 patients (17 males and 10 females) have a high incidence of *hGH-1A* deletion; of these, 1 family is Arab and 11 patients belong to 5 families. Five patients have a *GHRH-R* mutation in axon 11 and belong to two Arab families [10]. Data for two Arab patients diagnosed with *GHRH-R* mutation were not available.

The age at initiation of hGH treatment ranged between 0.1 and 21 years (mean 7 ± 4.3 years) and the duration of treatment was 1.5 to 15 years (mean 9.8 ± 4.8 years). The age of the patients at their last examination ranged between 20 and 66 years (mean 37.2 ± 11.6 years).

The mean (± SD) height of 19 male patients with cIGHD treated in childhood with hGH was 160.2 ± 10.6 cm (range 138–178 cm), and that of 10 female patients 146.4 ± 5.4 cm (range 139.4–156.5 cm). The short stature of some patients was due to the late initiation of the hGH treatment and/or lack of compliance.

The significant positive correlation between height and duration of hGH treatment is shown in Figure 1A. The majority of patients were obese. The subscapular skinfold thickness ranged from 7 to 40 mm (mean 20.42 ± 9.42 mm) (norm 10.5 mm) for men and 6–39 mm (mean 23.91 ± 9.49 mm) for women [16].

The mean BMI was 22.86 ± 4.8 for men and 23.75 ± 4.79 for women. Figure 1B illustrates the positive correlation between subscapular skinfolds and BMI ($R = 0.7429$ m, $P < 0.05$). The discrepancy between BMI and skinfold thickness in the obesity of congenital GH-deficient patients is due to underdevelopment of the muscular and skeletal systems. All patients achieved full sexual development.

Reliable measurements of testicular volume and stretched penile length were available for 11 and 10 patients respectively. Mean ± SD testicular volume was 14.3 ± 5.6 ml. The mean testicular volume for the Israeli mixed population is 17 ml [14] compared to 18.6 ± 4.8 ml for a European population [17]. The mean penile length was 11.6 ± 1.5 cm compared to the mean worldwide penis length of 13.24 ± 1.89 cm [18]. All patients had experienced sexual relations and 14 were married with children.

Twelve patients suffered from hyperlipidemia. Of them, four were treated with statins. Serum triglycerides were also elevated (> 200 mg/dl) in six patients. Fatty liver was demonstrated in one patient with hyperlipidemia, but not all had an abdominal ultrasonography.

Four patients developed type 2 diabetes after age 20. Their BMI was ≥ 26. One female patient developed gestational diabetes. Five patients developed cardiovascular disease (CVD). The diagnosis in all patients, except for one with congenital anomalies, was made after age 20.

Blood hemoglobin and red blood cell levels ranged between 11.2 and 16 g/dl, and 4.2 and 5.74 M/μl, respectively. No instances of anemia were registered. Creatinine levels ranged between 0.43 and 1.1 mg/dl. Additional findings in 11 patients were osteoporosis/osteopenia, hearing impairment, and vision impairment. Skull X-rays, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the skull and brain revealed a small sella in one patient.

None of the patients with cIGHD deficiency developed malignancies. One patient died at age 43 in a car accident.

The education status could be verified in 29 patients (19 men, 10 women). For 10 patients who were unavailable for questioning, the level of education was not stated in their records. The correlation between height SDS and education is shown in Figure 2. It shows that the taller patients tended to have a better education than shorter patients. The relationship between height and occupation is even stronger, as illustrated

Table 1. Genetic and clinical data of 32 adult patients with congenital isolated growth hormone deficiency

Patient no.	Sex	Ethnic origin	Genotype	Age at initiation of treatment (yrs)	Duration of treatment (yrs)	At study					
						Age (yrs)	Height (cm)	Height (SDS)	Weight (kg)	BMI	Subscapular skinfold (mm)
1[a]	Male	Middle East	hGH-1A del.	4.6	12.4	54	160.8	-2.09	67.4	26.1	23
2[a]	Male	Middle East		13.6	2.5	43	119.3	-8.33	31	21.8	26
3	Male	Middle East		2.5	13.6	48	158	-2.51	70	28.0	40
4	Male	Middle East		0.1	15.9	32	162.8	-1.79	66.5	25.1	23
5[b]	Male	Middle East		15.6	1.5	35	143	-4.77	36	17.6	12
6[b]	Male	Middle East		13.7	2	32	138	-5.52	40	21.0	14
7	Male	Ashkenazi		4	14.4	30	161.6	-1.97	67.5	25.8	28
8	Male	Ashkenazi		9	7.1	20	161.5	-1.98	50.5	19.4	12
9	Male	Ashkenazi		13.11	6.1	34	178	0.50	103	32.5	31
10	Male	Ashkenazi		4.6	13.5	35	176.7	0.30	59	18.9	7
11	Male	Israel		10.8	7.2	48	156	-2.81	55	22.6	21
12	Male	Arab		N/A	N/A	66	131.9	-6.44	35.5	20.4	22
13	Male	Russia-N. Africa		5.6	12.4	41	175.5	0.12	100	32.5	25
14	Male	Russia-USA		5	13	37	161	-2.06	52.5	20.3	8
15	Male	North Africa		6.8	11.5	46	153.6	-3.17	44.5	18.9	15
16[c]	Male	North Africa		3	18	27	172	-0.41	66.7	22.5	N/A
17[c]	Male	North Africa		1	23	24	166	-1.31	42	15.2	N/A
18[c]	Female	North Africa		11	5.9	50	141	-3.53	40	20.1	25
19[d]	Female	North Africa		7.1	7.9	41	144.6	-2.93	41.5	19.8	6
20[d]	Female	North Africa		12.6	3.6	52	144.8	-2.90	43	20.5	16
21[e]	Female	North Africa		11.4	4.1	52	144.1	-3.02	59.6	28.7	31
22[e]	Female	North Africa		3.11	11.8	23	146.3	-2.65	66.5	31.1	32
23	Female	North Africa		9	7	26	139.4	-3.80	50	25.7	20
24	Female	North Africa		4.5	9.8	43	152.3	-1.65	58	25.0	18
25	Female	Middle East		1.1	12.1	34	151	-1.87	54	23.7	27
26	Female	Middle East		1	12	40	139.5	-3.78	42	21.6	39
27	Female	Middle East		3.6	10.5	49	149.5	-2.12	66	29.5	32
28[f]	Female	Arab	GHRH-R mutation	6.7	9.8	21	156.5	-0.95	38	15.5	17
29[f]	Male	Arab		6.3	12.7	22	167	-1.16	56	20.1	17
30[f]	Male	Arab		6.6	10.5	33	170	-0.71	52	18.0	13
31[f]	Male	Arab		10.2	8.8	31	156.3	-2.77	72	29.5	38
32	Male	Arab		10	5.6	22	143.3	-4.72	49	23.9	13

[a]Family 1, [b]Family 2, [c]Family 3, [d]Family 4, [e]Family 5, [f]Family 6

in Figure 3. Patients with normal or close to normal height had academic, office or blue-collar employment, whereas those with marked growth retardation worked in sheltered workshops.

DISCUSSION

This is the first report of a large cohort of patients with congenital IGHD treated by hGH in childhood who were followed into adult age. In the literature there are few detailed descriptions of adult patients with proven congenital IGHD [3,4,8,19-21]. Of these, only one patient was treated in childhood [21]. Twenty patients from Brazil with *GHRH-R* mutation were treated as adults for a period of 6 months [22].

In contradistinction to the large cohort of patients from the north of Brazil [8] and the few patients from India – all of whom have a *GHRH-R* mutation – 27 of our patients originating from the Middle East have an incidence of *hGH-1A* deletions. Of interest is that none of our patients developed antibodies against hGH [10], as was also found in Japanese patients [23]. Isolated GH deficiency in our patients was proven not only by repeated stimulation tests but also by their low serum IGF-1 levels and normal values for other pituitary hormones. In our patients, the age and duration at the initiation of hGH treatment, and length of education, varied with the age at their immigration and the socioeconomic state of their families. Patients with early initiation of treatment and longer duration

Figure 1. [A] Correlation between duration of treatment and adult height (SDS) in 32 adults with congenital isolated growth hormone deficiency (cIGHD) **[B]** Discrepancy between subscapular skinfold thickness and BMI in 28 adult patients with congenital isolated growth hormone deficiency (cIGHD). The skinfold centiles are adjusted for age and gender from McDowell et al. [12]

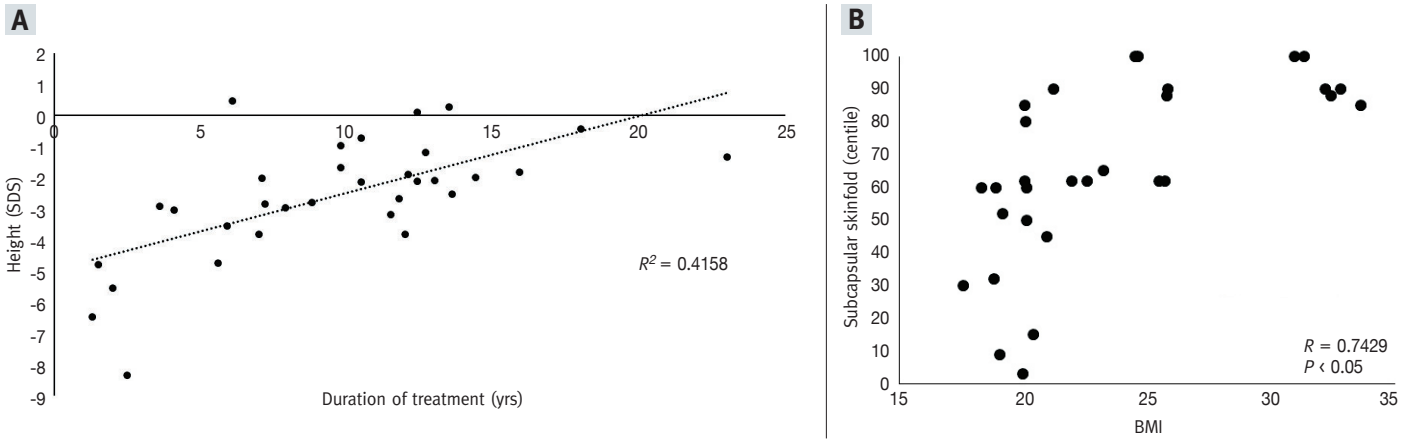


Figure 2. Adult height and education of 28 adults with congenital isolated growth hormone deficiency (cIGHD)

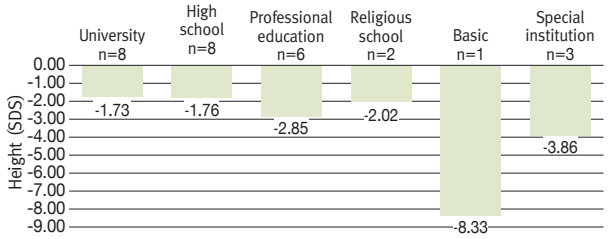
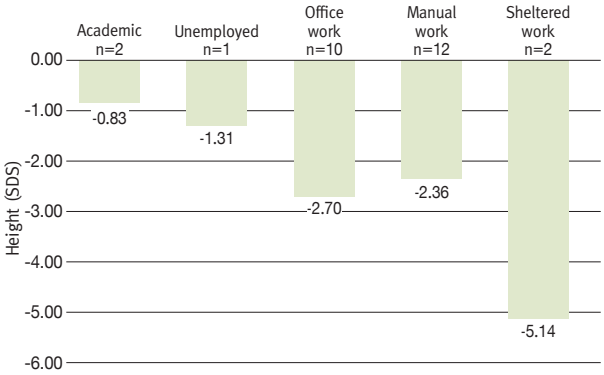


Figure 3. Adult height and occupation of 27 adults with congenital isolated growth hormone deficiency (cIGHD)



of treatment not only reached normal or close to normal height, but had a higher education and better occupations. It is of note that in two mentally retarded siblings, GH treatment had no effect on their mental development, probably due to additional genetic factors other than congenital GH deficiency.

All patients were overweight, even obese, as reflected by their subscapular skinfold thickness. This was not evident by BMI, which in longstanding GH deficiency underestimates the degree of adiposity due to the underdevelopment of the muscular and skeletal systems [24]. Obesity was also found in the Brazilian patients with cIGHD due to *GHRH-R* mutations [8,22].

None of our patients developed cancer, as expected by our findings that patients with congenital GH deficiency are protected from developing malignancies even if treated by hGH [25]. It is assumed that with a rise in the economic status of families with cIGHD, earlier and longer hGH treatment will not only improve the patients' height, educational level and occupation, but will also raise their quality of life.

CONCLUSIONS

Patients with congenital IGHD, if diagnosed and treated from an early age, can achieve normal height and complete higher education. Our patients, some of whom had immigrated as children from underdeveloped countries, did not achieve all the benefits of replacement hGH treatment in childhood and therefore some have deficits in education, employment and income. Since consanguineous marriages including those with congenital IGHD genes are now less frequent, and pregestational diagnosis in familial cases possible, it is expected that the prevalence of cIGHD of genetic origin will decrease.

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Capsule

Critical amino acid variations in hla-dqb1* molecules confer susceptibility to autoimmune thyroid disease in south India

The HLA-DQB1* region exhibits complex associations with autoimmune thyroid disease (AITD). **Ramgopa**l et al. checked AITD patients (Hashimoto's thyroiditis, HT = 180; Graves' disease, GD = 55) and age/sex-matched controls (n = 235) were genotyped for DQB1* alleles by PCR-SSP. Alleles DQB1*02:02, *06:03, *06:09, *03:02, and *03:03 showed an increased risk and *02:01, *05:02, and *06:02 showed a protection toward AITD. Multiple sequence alignment was used to determine the amino acid variations within the peptide-binding pockets of susceptible and/or protective DQB1* alleles. The authors observed susceptible associations for amino acids 'Glu^{86}(P < 0.0007)' and 'Leu87(P < 3.8 × 10–4)' in P1, 'Leu26(P < 4.0 × 10–12)' in P4, 'His9(P < 5.0 × 10–4)' and 'Ala57(P < 3.6 × 10–4)' in P9 toward HT; and 'Gly86(P < 0.0004)' in P1 and 'Asp57(P < 1.9 × 10–4)' in P9 towards GD. Protective associations were observed for amino acids 'Ala86(P < 8.2 × 10–6)' and 'Tyr87(P < 0.0003)' in P1, 'Gly26(P < 4.9 × 10–5)' and 'Ser74(P < 4.9 × 10–5)' in P4, 'Phe9(P < 0.0007)' and 'Ser57(P < 0.0016)' in P9 towards HT. Thus, the study revealed that DQB1* alleles and putative amino acid residues play an important role in susceptibility toward AITD in south India.

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Eitan Israeli

"It is a funny thing about life: if you refuse to accept anything but the best you very often get it"

W. Somerset Maugham (1874–1965), British playwright, novelist, and short story writer