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CASE REPORT

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Long-term Growth Hormone Therapy in a Patient with *IGF1R* Deletion Accompanied by Delayed Puberty and Central Hypothyroidism

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What is already known on this topic?

Insulin-like growth factor-1 (IGF-1) is the main driver of growth during prenatal life. Patients with IGF-1 receptor (IGF1R) defects exhibit variable phenotypic features. The most common symptom is pre- and post-natal growth retardation, followed by microcephaly, developmental delay, facial dysmorphism and extremity anomalies. Recombinant human growth hormone (rhGH) has been used in patients with IGF1R defects with variable treatment response.

What this study adds?

Long-term rhGH with an early initiation may have more beneficial effects in terms of induction of growth. Regarding the complex physiological effects of IGF1, patients should be followed for hormone deficiencies, such as hypogonadism and hypothyroidism.

Abstract

Insulin-like growth factor-1 (IGF-1) is the main driver of growth during prenatal life and acts through IGF-1 receptor (IGF1R). Patients with IGF1R defects exhibit variable phenotypic features. A 10.9-year-old boy presented with severe short stature, microcephaly, minor dysmorphic features and mental retardation. Genetic analysis for *IGF1R* revealed heterozygous deletion of the complete *IGF1R*. At the age of 12.3 years, daily subcutaneous recombinant human growth hormone (rhGH) was started and continued for a total of 5.7 years in two courses with improvement of height velocity as well as final height. Puberty was delayed and eventually he did not achieve full puberty, suggesting partial hypogonadotropic hypogonadism. Hypothyroidism initially developed during rhGH therapy. However, low T4 levels persisted after cessation of rhGH therapy and thus central hypothyroidism is a likely diagnosis. rhGH has partial effect for induction of growth in cases with *IGF1R* defects. However, long-term treatment with an early initiation may have more beneficial effects. In addition, patients with *IGF1R* defects should be followed for delayed puberty-hypogonadism, and hypothyroidism.
Keywords: IGF1R, deletion, growth hormone therapy, delayed puberty, hypothyroidism

Introduction

Growth factors are crucial for prenatal growth. Insulin-like growth factor-1 (IGF-1), which has structural homology with proinsulin, is the main driver of growth during prenatal life and acts through IGF-1 receptor (IGF1R). The gene coding for IGF1R, *IGF1R*, is located on the distal part on the long arm of the chromosome 15 (15q26.3) (1). In animal models, *IGF1R* null mice exhibited severe growth restriction (45% of normal size) and died soon after birth due to lung and

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respiratory muscle hypoplasia, ossification was delayed, epidermis was underdeveloped and there were central nervous system anomalies (2). Since the first description of patients with *IGF1R* mutation who had intrauterine growth retardation, poor postnatal growth, developmental delay and microcephaly, cumulative evidence has shown that the phenotypic characteristics of patients with *IGF1R* defects can vary widely (3,4,5). 15q26 terminal deletions lead to contiguous gene syndrome and there is no clear genotype-phenotype correlation with significant inter- and intra-familial variability. Homozygous or compound heterozygous mutations seem to cause more severe phenotype (3,6,7). Endocrine consequences of *IGF1R* defects other than short stature, such as delayed puberty, premature ovarian failure, and growth hormone deficiency have been reported very rarely (5,8,9,10,11). Central adrenal insufficiency and hypothyroidism have not been reported previously.

Recombinant human growth hormone (rhGH) is approved by the Food and Drug Administration and the European Medicine Agency for treatment of children born small for gestational age (SGA). rhGH has been used in patients with *IGF1R* defects with variable treatment response. rhGH may be discontinued due to no improvement in growth velocity, continued without catch-up growth (3,10,12,13,14,15) or result in mild catch-up growth (13,14,16).

We report a boy with 15q terminal deletion, who presented with severe growth retardation, microcephaly, and developmental delay who also had delayed puberty and central hypothyroidism. We also aim to report the long-term results of rhGH therapy.

Case Report

A 10.9-year-old boy was referred for short stature. He was born at term to healthy, nonconsanguineous parents with a reportedly normal birth weight but his birth length was unknown. Maternal and paternal heights were -2.8 standard deviation score (SDS) (146.7 cm) and -2.0 SDS (163.7 cm), respectively, and midparental height was -2.3 SDS (161.7 cm). There was no feeding difficulty during infancy. He was able to say his first words and walk at the age of 1.5 and 2.5 years, respectively. He had been evaluated at another health center for short stature at the age of six years and thyroid hormones, growth factors, and celiac antibodies were normal.

He presented with a height of -5.3 SDS (108.3 cm), a weight of -4.9 SDS (18.5 kg), and a head circumference of -4.1 SDS (48 cm) at the age of 10.9 years old. He had proportional severe short stature with no dysmorphic features, except for a triangular face. He was prepubertal. Neurological examination was unremarkable, except for mental retardation detected in the Wechsler Intelligence Scale for Children-Revised test (intelligence quotient 65). Bone age determined by the Greulich and Pyle method was five years. Total blood count and blood chemistry were normal, as was a skeletal survey. In the endocrine work-up, IGF-1 was 240.2 ng/mL (close to 0 SDS), insulin-like growth factor binding protein-3 was 4228.7 ng/mL (0.43 SDS). GH stimulation test showed a peak GH response of 10.3 ng/mL. Other pituitary hormones, including adrenocorticotropic hormone (ACTH) [19.5 pg/mL (normal range 0-46)], cortisol (8.5 µg/dL), prolactin [9.3 ng/mL (normal range 2.5-18)], free T4 [1.19 ng/dL (normal range 0.9-1.7)], and thyroid stimulating hormone (TSH) [2.4 uIU/mL (normal range 0.3-4.2)] were normal. He had primary nocturnal enuresis and renal ultrasound revealed kidney size in the lower range for age.

Karyotype analysis was 46,XY. Genetic analysis for *IGF1R* was performed in Leiden University Medical Centre. MLPA analysis of the coding region (exon 1-21) revealed heterozygous deletion of the complete *IGF1R* gene. SNP microarray identified a 3.3 Mb terminal deletion on the long arm of the chromosome 15 (15q26.3x1) which included *IGF1R* and there was also a terminal duplication with a maximum size of 2.6 Mb on the short arm of chromosome 9 (9p24.3p24.2x3). The terminal 9p duplication and the terminal 15q deletion suggest the presence of an unbalanced reciprocal translocation between the short arm of chromosome 9 and the long arm of chromosome 15. MLPA and SNP microarray were normal for chromosome 9 and 15 in both mother and father.

At the age of 12.3 years, height was -5.27 SDS (114.2 cm), weight -5.4 SDS (19.5 kg) and growth velocity 4.1 cm/year. His IGF-1 was 383 mg/dL (0.5 SDS). Daily subcutaneous rhGH was started at a dose of 0.21 mg/kg/week (Figure 1) and the dose was increased to 0.30 mg/kg/week after three months. Treatment was continued for eighteen months. During this period his growth velocity was 7.1 cm for the first year (height was 121.3 cm, -4.67 SDS), which then slowed to 2.2 cm during the next six months. Treatment was withdrawn for slow growth velocity. Nine months later, rhGH treatment was restarted at a dose of 0.30 mg/kg/week due to slow growth rate (2.9 cm in nine months). During rhGH therapy, serum IGF-1 levels varied between + 1 and + 2 SDS.

At the age of 14.8 years, testes were 6 mL bilaterally and increased to 8 mL at the age of 15.7 years, but did not progress afterwards. At the age of 16.5 years with an observation of delayed puberty [testes volumes 8 mL bilaterally, follicle-stimulating hormone (FSH) 5.27 mIU/mL (normal range 1.3-19.2), luteinizing hormone (LH) 0.21 mIU/mL (normal range 1.8-8.6), testosterone 29.4 ng/dL (normal range 220-800)] intramuscular testosterone (propionate 30

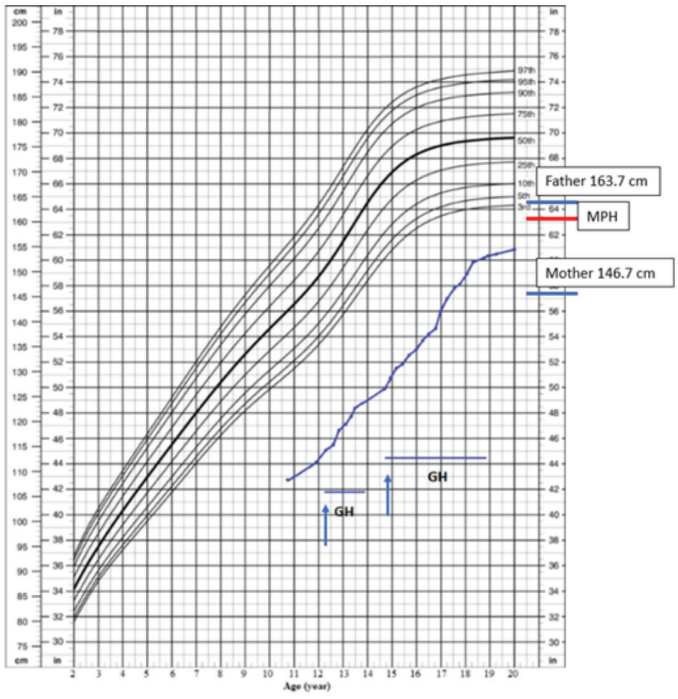

Figure 1. Growth chart of the patient. The patient had two courses of growth hormone therapy. Normative data for boys is from the Centers for Disease Control and Prevention

GH: growth hormone

mg, phenylpropionate 60 mg, isocaproat 60 mg, decanoate 100 mg) was commenced at a dose of 50 mg/monthly.

At the age of 17.3 years, while he was on rhGH, thyroid function tests revealed hypothyroidism [TSH 2.13 uIU/mL, (normal range 0.4-5.3) with free T4 0.51 ng/dL, (normal range 0.6-1.1)]. Central adrenal insufficiency was also diagnosed [ACTH 32.5 pg/mL, peak cortisol during low dose ACTH stimulation test was 16.8 µg/dL (N: > 18.9)]. Thus, both hydrocortisone and levothyroxine were started. On pituitary magnetic resonance imaging, the height of the pituitary gland was 4.5 mm, and a pars intermedia cyst 2 mm in diameter was present on the anterior region of neurohypophysis.

At the age of 18.8 years, his height was -3.26 SDS (152.9 cm) and weight was -3.44 SDS (44.6 kg). His height increased 0.8 cm in the last 6 months, bone age was 16 years and rhGH treatment was withdrawn. After 5.7 years of rhGH treatment in two courses, he had a height gain of 2.01 SDS. Testis volumes increased to 10 mL bilaterally [FSH 7.1 mIU/mL (normal range 0.9-11.9), LH 1.5 mIU/mL (normal range 0.5-12.0), testosterone 152.2 ng/dL (normal range 151-794) two weeks after the last dose of testosterone], and testosterone treatment was withdrawn as well. In addition, the hypothalamic-pituitary-adrenal axis was rechecked, the peak cortisol response to low dose ACTH test was 18.9 µg/dL and hydrocortisone was discontinued with instructions for stress coverage. At the age of 19.5 years the size of his testes and testosterone concentrations had not increased [testes 10 mL bilaterally, FSH 8.05 mIU/mL (normal range 0.9-11.9), LH 0.84 mIU/mL (normal range 0.6-12.1), testosterone 156.9 ng/dL (normal range 47-981)], so testosterone was restarted. During the last follow-up when he was 20 years old, height was -3.06 SDS (154.8 cm), weight 45 kg (-3.45 SDS), and he had not been using levothyroxine for three months. Thyroid function test still suggested central hypothyroidism [TSH 3.8 mIU/mL, (normal range 0.27-4.2); free T4 0.88 ng/dL, (normal range 0.93-1.7), and free T3 3.26 ng/L (2-4.4)].

Discussion

We report a boy with *IGF1R* deletion presenting with severe short stature, microcephaly, mental retardation and mild dysmorphic features. Growth hormone therapy for a total of 5.7 years in two courses improved height velocity, as well as final height. Moreover, puberty was arrested and eventually he could not complete puberty, suggesting partial hypogonadotropic hypogonadism. Hypothyroidism developed during GH therapy which may be associated with isolated GH deficiency during GH therapy (17). However, low T4 levels persisted after cessation of GH therapy and thus central hypothyroidism is a likely diagnosis.

Patients with *IGF1R* defects exhibit variable phenotypic features. The most common symptom is pre- and post-natal growth retardation, followed by microcephaly, developmental delay, facial dysmorphism and anomalies of the extremities. Although birth weight or height below -2 SDS were used as the inclusion criteria in studies evaluating *IGF1R* defects (15), patients have shown wide variation in these parameters; birth weight between -4.1 and -0.8, birth length -5.8 and -1.0, and head circumference -5.7 and 0.8 SDS (3,6,12,14). Patients with terminal 15q deletions may exhibit additional features involving other organ systems, such as cardiac, genitourinary, respiratory, and ocular (7,14) disorders, attributed to defects in contiguous genes, some of which may impact growth. However, the presented patient had only mild dysmorphic features, neurodevelopmental delay, and small-normal kidneys without involvement of other major organ systems.

rhGH therapy has been recommended for patients with *IGFR1* defects in higher than usual doses to overcome receptor resistance (15). Growth promoting effects of rhGH is less pronounced in comparison to patients with SGA, and response is quite variable among patients with *IGF1R* defects (18). Although the rhGH response in the first year is lower than in SGA patients, the constant growth velocity in the following years may suggest the importance of

long-term treatment (18). The dose of rhGH is expected to be important, however, Göpel et al. (18) did not find any association between dose and treatment response. In addition, it has been a matter of debate whether genotype influences rhGH treatment response. Walenkamp et al. (4) found no difference in 3-year rhGH response between twelve patients with mutations and seven with deletions who received rhGH therapy at similar ages. Göpel et al. (18) reported that the ratio of patients with a good response to treatment was higher in carriers of mutations within the intracellular part of IGF1R compared to the extracellular part. However, it should be emphasized that number of patients were limited due to the rarity of *IGF1R* defects.

We reviewed 28 patients with *IGF1R* defects who received rhGH (Table 1). Thirteen (46%) had terminal 15q deletions or ring chromosome, fourteen (50%) heterozygous mutations, and one (4%) compound heterozygous mutation. Sixty-one percent of patients with terminal 15q deletions or ring chromosome, and 35% of patients with *IGF1R* mutations exhibited ≥0.5 SDS increase in height during the first year of rhGH. Sixty-nine percent of patients with terminal 15q deletions or ring chromosome, and 42% of patients with mutations had a height gain of ≥1 SDS based on the last evaluation or final height. One of the two patients with the worst treatment response had a compound heterozygous mutation and the other with 15q26 deletion had hypoplastic left heart. Forty-six percent of patients who did not gain ≥0.5 SDS in the first year of treatment achieved ≥1 SDS with prolonged treatment. The presented patient had a height gain of 0.6 SDS in the first year of rhGH treatment, and 2.01 SDS overall with a 5.7 year treatment duration.

The presence of IGF-1 and IGF-1R has been demonstrated in various cells, including the pituitary (19). IGF-1 is a mitogenic hormone that induces proliferation and differentiation of various cells and participates in physiological regulation. IGF-1 is the key modulator of GH action and also participates in regulation of the hypothalamo-pituitary-gonad (HPG) axis. The expression of GH and IGF1 receptors in the elements of HPG axis and reproductive organs has been demonstrated in molecular studies. GH and IGF1 participate in various stages of maturation of the reproductive axis, including intrauterine stages, mini-puberty and onset of puberty. Cryptorchidism was reported in two patients with *IGF1R* deletion (7,20). Although contiguous gene syndrome cannot be excluded as an etiology of cryptorchidism, IGF1R haploinsufficiency could still be the causative factor, highlighting intrauterine effects. *In vitro* animal models showed that IGF-1 both induces proliferation of gonadotrophs and secretion of gonadotropins (21), which underlines the importance of growth factors for induction of puberty and its progression. IGF-1 participates in testis and ovary function, in terms of Sertoli and granulosa cell survival and production of gonadal steroid hormones (22,23). Hypergonadotropic hypogonadism was also reported in patients with *IGF1R* defects (5,24). It is interesting that cases with *IGF1R* duplication had azoospermia. These data suggest that an intact IGF-1 system is necessary for the maturation and maintenance of the reproductive system. The presented patient exhibited features of hypogonadotropic hypogonadism. Puberty started at the age of 14.8 years, and did not progress appropriately, so sex steroid replacement was established. Patients with delayed puberty were reported previously with *IGF1R* defects, but none of them required sex steroids since puberty progressed spontaneously (8,9).

One of the consequences of rhGH therapy is alteration of thyroid hormones. GH induces the activity of deiodinase, probably type 2, thus free T4 level may decrease and free T3 level may increase during rhGH therapy. TSH concentration is not expected to increase in the face of increased free T3. Thus rhGH therapy can either mimic or unmask central hypothyroidism (17). Our patient developed central hypothyroidism during rhGH therapy, however, this condition continued even after cessation of rhGH. Since *IGF1R* expressed in pituitary somatotrophs participates in negative feedback on the somatotropic axis, receptor resistance may disrupt negative feed-back leading to an increase in GH levels. Elevation in GH levels may induce somatostatin from the hypothalamus which is a weak inhibitor of TSH (25). Studies using salmon pituitary cells have shown that IGF-1 can stimulate thyrotropin beta subunit transcript in a dose-dependent manner (26). In addition, the GH-IGF1 axis has important effects on thyrocytes. In *in vitro* animal studies, GH and IGF-1 showed synergistic effects with TSH on thyroid gland growth and hormone production (27). Thus, *IGF1R* defects may be expected to impact thyroid function at multiple levels. Interestingly, no patient with an *IGF1R* defect and hypothyroidism has been reported to date. Thus, it is not possible to ensure that alterations in thyroid function in the current patient is a direct consequence of IGF-1 resistance. Also, a pars intermedia cyst was detected on MRI. Pars intermedia cysts, remnants of Rathke's pouch, rarely causes symptoms, with symptoms being related to mass effect and/or pituitary hormone deficiency (28). Some reports suggested a positive correlation between cyst size and impairment of pituitary function (29), while other reports suggest an association between symptoms and chronic inflammation around the cyst wall (28). However, small cysts are expected to be asymptomatic and detected incidentally or at autopsy (29), and the frequency of pituitary hormone deficiency increases in ≥10 mm cysts (30). Therefore, pituitary hormone deficiency would not be expected in a 2 mm diameter pars intermedia cyst.

Table 1. Features of genotype, auxology and phenotype of patients who were given rhGH

Author (year)	Deletion/mutation	Gender (F/M)	Birth weight/ length/head circumference	Age at first evaluation; height (SDS)	Age at the start of rhGH (year); height (SDS)	Duration (year)	Height gain at the first year of rhGH (SDS)	Age (year) at last evaluation; height (SDS)	Final height	Other features	Affected family member	Other hormonal deficiencies
Ho et al. (31)	46,XX,r(15) (p11q26.3)	F	-0.8 / NA / NA	0.4; -5.6	1.8; -5.3	12.4	+1	NA; -2.1	-2.1	DD	NA	NA
Ho et al. (31)	46,XX,r(15) (p13q26.2)	F	-1.6 / NA / -3.3	0.5; -4.4	2.6; -3.3	12.2	+0.5	NA; -2.5	-2.5	Hip dislocation, DD	NA	NA
Ho et al. (31)	46,XY,del(15) (q26.3)	M	-1.6 / NA / NA	1.5; -3.7	5.2; -4.0	11.8	+0.7	NA; -2.6	-2.6	Bilateral talipes, DD	NA	NA
Ester et al. (10)	15q26.3 deletion, exons 3-21	M	-1.9 / -2.2 / NA	3.0; -3.84	7; -3.57	10	+0.83	17; -1.89	NA	DD, DF, EA, HL	No	NA
Gkourogianni et al. (32)*	c.3364G > T p.Gly1122Cys	M	NA	NA	9.1; -3.5	9.6	+0.2	18.7; -1.8	-1.8 SDS	No DF.	Mother; -2.1 SDS	DP
Abuzzahab et al. (3)	Compound heterozygousArg108Gln, Lys115Asn, exon 2	F	-3.5 / NA / NA	NA	4.1 yr, for 2 years and at 8.7 yr old restarted	7.9 yrs in two courses	+0.17 in the first course	NA	-4.8 SDS	DD and psychiatric disorders		Menarche at the age of 12.5 yr
Walenkamp et al. (13)	15q26.2-qter	F	-3 / -1.3 / -2	4.5; -3.5	5.3; NA	6.7	NA	NA	-1.6 SDS	DD	No	NTF. Puberty started at the age of 12.8 yr
Yang et al. (33)*	c.3740T>C, p.M1247T	F	-1.9 / NA / NA	2.1; -3.85	2.8; -3.36	6	+0.6	8.8; -2.4	NA	No DD	Mother; -1.96 SDS	NA
Ho et al. (31)	46,XX,del(15) (q26.2)	F	-2.9 / NA / -3.7	3.0; -4.9	5.0; -4.9	5.8	+0.1	NA; -4.9	-4.9	Hypoplastic left heart, DD, dysplastic kidney	NA	NA
Leal et al. (15)	c.1531C>T, p.Arg511Trp, exon 7	F	-2.5 / NA / NA	5.8; -2.7	8.4; -2.9	5	+0.9	13.3; -1.7	NA	No DD Mild DF	Mother; -2.9 SDS	NP
Veenma et al. (14)**	15q26.3 microdeletion	M	-1.7 / -2.3 / 0.88	12; -4.2	13.8; NA	4.6	+0.1	NA, the overall catch-up growth was +1.8 SDS	NA	DD, DF, café-au-lait, strabismus, refraction anomalies of lens	Mother; -4.42 SDS	NP
Labarta et al. (12)	c.1549A>T, p.Y487F, exon 7	F	-3.46 / -4.9 / -5.7	1.5; -2.84	3.4; -3.19	4.1	+0.31	7.5; -2.39	NA	Slightly retarded	Mother; -1.6 SDS	Mother menarche at the age of 13 yr
Ester et al. (10)	15q26.3 deletion, exons 1-21	F	-1.28 / -2.21 / NA	2.3; -3.46	4; -3.42	4	+1.02	8.3; -1.68	NA	DD, DF, EA, HL, hyperlaxity	No	NA

Table 1. Continued

Author (year)	Deletion/mutation	Gender (F/M)	Birth weight/ length/head circumference	Age at first evaluation; height (SDS)	Age at the start of rhGH (year); height (SDS)	Duration (year)	Height gain at the first year of rhGH (SDS)	Age (year) at last evaluation; height (SDS)	Final height	Other features	Affected family member	Other hormonal deficiencies
Nuutinen et al. (34)	46,XY, r(15) (pll.2q26.2)		-3.2 / -4.0 / NA	0.6; -6.2	2.2; -6.2	2	+1.2	4.2; -4.4	NA	DD, DF, café-au-lait	NA	NTF
Choi et al. (7)*	c.420del, p.Ala110fsX20, in exon 2	F	-2.1 / NA / NA	6.8; -3.56	8; -3.56	1	+1.18	9; -2.38	NA	No DD or DF	Father; -4.19 SDS	NTF
Ho et al. (31)	46,XX,r(15) (p13q26.3)	F	-2.5 / NA / -2.0	0.5; -3.0	3.3; -3.8	1.0	+0.8	4.3; -3.0	NA	DD, DF	NA	NA
Choi et al. (7)*	c.420del, p.Ala110fsX20, in exon 2	M	-1.96 / NA / NA	9.5; -3.47	10.5; -3.42	1	+0.64	11.5; -2.78	NA	NA	Father; -4.19 SDS	NA
Ho et al. (31)	46,XY,del(15) (q26.3)	M	-1.4 / NA / NA	3.2; -4.8	6.2; -4.6	1.6	+0.6	7.8; -3.4	NA	DD, DF	NA	NA
Raile et al. (35)	Arg59Ter, exon 2	M	-3.5 / -5.8 / NA	1.1; -3.8	6.4; -2.51	2	+0.55	8.5; -1.5	NA	DD, DF	Mother; -2.6 SDS	NTF, NAF, normal prolactin
Wallborn et al. (36)*	c.1886T > A, p. V599E	F	-2.26 / -1.82 / < 3p	NA	7.42; -2.27	1.5	+0.43	9.02; -1.4	NA	DD, ADHD	Mother; -3.3 SDS	NTF
Mahmoud et al. (16)*	15q26.2q26.3 deletion	M	-3 / -3.2 / NA	2.5; -9.3	3.4; -3.4	2.6	+0.33	6; -1.5	NA	Mild DD, DF	No	NTF
Gkourogianni et al. (32)*	c.3364G > T p.Gly1122Cys	M	-2.0 / -1.6 / -2.15	6.8; -2.3	7.9; -2.2	2.6	+0.23	10.5; -1.15	NA	Attention deficit disorder	Father; -1.8 SDS	NA
Ho et al. (31)	46,XX,del(15) t(15;16) (q26.1:q22.3)	F	-1.6 / NA / NA	5.0; -5.4	12.4; -5.9	2.2	+0.2	14.6; -5.7	NA	DD, EA, VSD, subglottic stenosis	NA	NA
Fang et al. (37)*	19Dup in exon 18	M	-3.04 / -1.5 / NA	9.6; -3.6	10; -3.65	2	+0.03	12; -3.05	NA	Bifid uvula, ADHD	Mother; -4.6 SDS	NTF, NAF
Inagaki et al. (38)	c.1577G > A, p.R481Q, exon 7	F	-3.1 / -4.9 / NA	13.6; -5	NA	0.5	0 SDS	NA	NA	Mild DF	Mother; -5.7 SDS	T2P2 at presentation
Mohn et al. (39)	c.1161C > A, p.Tyr387X, exon 5	M	-2.03 / -3.08 / NA	4; -4.58	8; NA	1	No improvement in GV	18; -3.08	NA	No DD	Father; -2.94 SDS	NP
Kawashima et al. (40)	c.3405C > A	F	-1.5 / -2.5 / NA	6; -3.0	6; -3.0	3	NA	9; -1.5	NA	DD	Mother; -4.0 SDS	NA
Kawashima et al. (40)	c.1382G > T, R431L	F	-1.8 / -3.2 / NA	3; -2.9	5; -3.0	2	NA	8; -2.7	NA	No DD	Mother; -1.2 SDS	NA
Fujimoto et al. (41)	c.3798C > T, p.Q1250X, exon 21	M	-3.3 / -2.1 / -3.7	3; -3.2	6; -3.1	2	NA	8.7; -2.6 (at the end of the rhGh -2.5)	NA	No DD	No	NA

*GV, height SDS calculated from growth charts. **In the first 2 years also received GnRHa.

ADHD: attention deficit hyperactivity disorder, CA: cardiac anomaly, DD: developmental delay, DF: dysmorphic features, DP: delayed puberty, EA: extremity anomalies, GV: growth velocity, HL: hearing loss, MR: mental retardation, NAF: normal adrenal function, NP: normal puberty, NTF: normal thyroid function, F/M: female/male, rhGH: recombinant human growth hormone, SDS: standard deviation score, yr: year, NA: not applicable

IGF-1 immunoreactivity was detected in the same secretory granules of the corticotroph cells, indicating a concomitant secretion and release of both hormones (19). Despite the coexistence of both hormones, recent studies showed no effect of IGF-1 on ACTH secretion and corticotroph responsiveness to CRH (19). Instead, corticotroph cells may require IGF-1 to protect them against apoptosis, especially in stressful situations (19). The first low dose ACTH test that was performed, before levothyroxine treatment, revealed an inadequate serum cortisol peak, and the results of the second were just above the lowest reference range. We could not definitively exclude the diagnosis of central adrenal insufficiency, due to the technical limitations of the low dose ACTH test and its lower sensitivity and specificity compared to the insulin tolerance test. However, the lack of protective effects of IGF1 could make these patients vulnerable to apoptosis of corticotroph cells.

Conclusion

In conclusion, rhGH has partial beneficial effect on growth in cases with *IGF1R* defects if long-term, early-onset treatment has been instituted. Even if the treatment response to rhGH is relatively poor during the first year, it is important to continue the treatment since 42 % of the patients have a height gain of more than 1 SDS in the long-term. In addition, patients with *IGF1R* defects should be followed for later development of hormone deficiencies.

Ethics

Informed Consent: Written informed consent was collected from the patient.

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Footnotes

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