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Abstract

GH insensitivity (GHI) or resistance is defined as the absence of an appropriate growth and metabolic response to endogenous growth hormone (GH) or to GH administered at physiologic replacement dosage. The genetic disorders that interfere with the response to GH include mutations affecting the GH receptor (GHR), serum transducers, and activator of transcription 5b (STAT5b), acid-labile subunit (ALS), insulin-like growth factor I (IGF-I), and IGF-I receptor.

Keywords

Growth hormone (GH) receptor (R) • GHR gene mutation • Laron syndrome • GH-binding protein (BP) • Insulin-like growth factor I • IGFBP • Recombinant IGF-I • Serum transducers and activator of transcription 5b • Acid-labile subunit • IGF-I R • Noonan syndrome

The Growth Hormone–Insulin-like Growth Factor-I Axis

Growth hormone (GH) synthesis and secretion by the anterior pituitary somatotrophs is under the control of stimulatory GH-releasing hormone (GHRH) and inhibitory somatostatin (SS) from the hypothalamus (Fig. 2.1). Other GH secret-

agogues (e.g., ghrelin and various synthetic hexapeptides) may also play a role. The stimulation and suppression of GHRH and SS result from a variety of neurologic, metabolic, and hormonal influences. Of particular importance to discussions of GHI is the feedback stimulation of SS by insulin-like growth factor (IGF)-I, with resultant inhibition of GH release [1].

GH bound to the soluble GH-binding protein (GHBP) in the circulation is in equilibrium with approximately equal amounts of free GH. Because the binding sites for the radioimmunoassay of GH are not affected by the GHBP, both bound and unbound GH are measured [2]. GHBP is the proteolytic cleavage product of the full-length membrane-bound receptor molecule [3].

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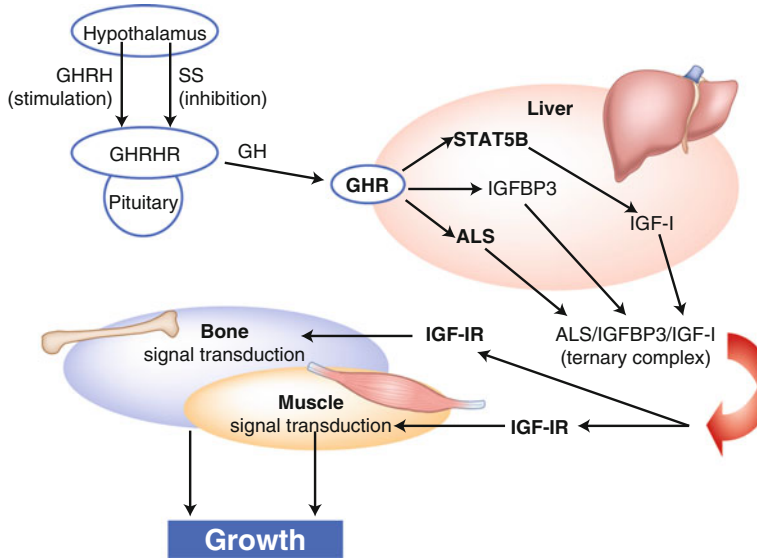


Fig. 2.1 Simplified diagram of the hypothalamic-pituitary-GH/IGF-I axis, showing mutational targets resulting in GH insensitivity indicated in **bold**

This characteristic permits assaying circulating GHBP as a measure of cellular-bound GHR, which usually correlates with GHR function [1].

The GH molecule binds to a molecule of cell surface GHR, which then dimerizes with another GHR molecule in the extracellular domain, so that a single GH molecule is enveloped by two GHR molecules [4]. The intact receptor lacks tyrosine kinase activity but is closely associated with JAK2, a member of the Janus kinase family. JAK2 is activated by binding of GH with the GHR dimer, which results in self-phosphorylation of the JAK2 and a cascade of phosphorylation of cellular proteins. Included in this cascade are signal transducers and activators of transcription (STATs), which couple ligand binding to the activation of gene expression, and mitogen-activated protein kinases (MAPK). STAT5b is the most important of these activator proteins. This is a mechanism typical of the growth hormone/prolactin/cytokine receptor family that includes receptors for erythropoietin, interleukins, and other growth factors [2].

The effect of GH on growth is indirect, via stimulation of IGF-I production in the liver and

growing tissues, particularly bone and muscle [1]. Hepatic (endocrine) IGF-I circulates almost exclusively bound to IGFBPs, less than 1% being unbound. The IGFBPs are a family of six structurally related proteins with a high affinity for binding IGF. At least four other related proteins with lower affinity for IGF peptides have been identified and are referred to as IGFBP-related proteins [5, 6]. IGFBP3 is the most abundant IGFBP, binding 75–90% of circulating IGF-I in a large (150–200 kDa) complex which consists of IGFBP-3, an acid-labile subunit (ALS), and the IGF molecule. Both ALS and IGFBP3 are produced in the liver as a direct effect of GH. The ALS stabilizes the IGF-IGFBP3 complex, reduces the passage of IGF-I to the extravascular compartment, and extends its half-life. The remainder of bound IGF is in a 50-kDa complex with mostly IGFBP-1 and IGFBP-2.

IGFBP-1 production is highly variable, with the highest concentrations in the fasting, hypoin-sulinemic state. The circulating concentration of IGFBP-2 is less fluctuant and is partly under the control of IGF-I; levels are increased in GHR-deficient states but increase further with IGF-I

Table 2.1 Conditions characterized by unresponsiveness to endogenous or exogenous growth hormone: clinical and biochemical characteristics

Condition	Growth failure	GH	GH-binding protein	IGF-I	IGFBP3
<i>Genetic</i>					
GHR def recessive forms	Severe	Elevated	Absent–low ^a	Very low	Very low
GHR def dom neg forms	Mild–moderate	Elevated	Increased	Very low	Low normal
STAT5b mutation	Severe	Elevated	Normal	Very low	Very low
ALS mutation	None–moderate	Normal	Normal	Very low	Very low
IGF-I gene mutation	Severe	Elevated	Normal	Absent/high ^b	Low/normal
IGF-I receptor mutation	Mild–moderate	Normal–elevated	Normal	Normal–elevated	Normal–elevated
<i>Acquired</i>					
GH inhib antibodies	Severe	Absent	Normal	Very low	Low
Malnutrition	None to severe	Elevated	Decreased	Variable	Variable
Diabetes mellitus	None to mild	Elevated	Decreased	Decreased	Increased
Renal disease	Mild to severe	Normal	Decreased	Normal	Increased
Hepatic disease	Mild to severe	Elevated	Normal–increased	Decreased	Normal

^aIncreased in mutations of or near the transmembrane domain of the GH receptor

^bAbsent with partial IGF-I gene deletion; very high with abnormal IGF-I

therapy of such patients [7]. The IGFBPs modulate IGF action by controlling storage and release of IGF-I in the circulation, by influencing the binding of IGF-I to its receptor, by facilitating storage of IGFs in extracellular matrices, and by independent actions [5].

Autocrine and paracrine production of IGF-I occurs in tissues other than the liver. In growing bone, GH stimulates differentiation of pre-chondrocytes into chondrocytes able to secrete IGF-I, which stimulates clonal expansion and maturation of the chondrocytes, with growth. It is estimated that at least 20% of GH-stimulated growth results from this autocrine/paracrine IGF-I mechanism [8].

IGF binding involves three types of receptors: the structurally homologous insulin receptor and type 1 IGF receptor and the distinctive type 2 IGF-II/mannose-6-phosphate receptor. Although the insulin receptor has a low affinity for IGF-I, IGF-I is present in the circulation at molar concentrations that are 1,000 times those of insulin. Thus, even a small insulin-like effect of IGF-I could be more important than that of insulin itself, were it not for the IGFBPs that control the availability and activity of IGF-I. In fact, intravenous infusion of recombinant human IGF-I (rhIGF-I)

can induce hypoglycemia, especially in the IGFBP3-deficient state [9].

GH Insensitivity

GH insensitivity (GHI) or resistance is defined as the absence of an appropriate growth and metabolic response to endogenous GH or to GH administered at physiologic replacement dosage [1]. Table 2.1 lists the known conditions associated with GH resistance and their clinical and biochemical features. The genetic disorders that interfere with the response to GH include mutations affecting the GH receptor (GHR), STAT5b, ALS, IGF-I, and IGF-I receptor (Fig. 2.1).

The conditions that have been associated with acquired GHI may not demonstrate low levels of IGF-I, or even consistent growth failure. Acquired GH resistance occurs in some patients with GH gene deletion for whom injections of recombinant human GH stimulate the production of GH-inhibiting antibodies [10]. Growth failure associated with chronic renal disease is thought to be related to increased concentrations of IGFBPs with normal or elevated GH and usually normal total IGF-I levels [11].

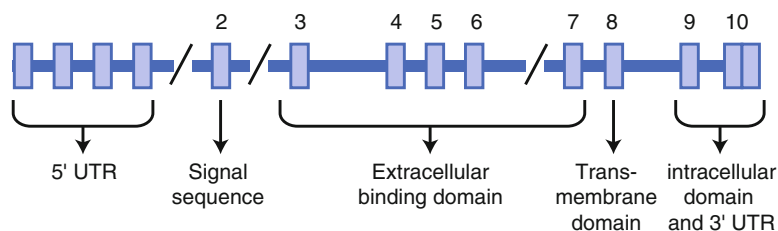


Fig. 2.2 Representation of the GHR gene. The *black horizontal line* represents intron sequence; *breaks in lines* indicate uncloned portions of the intron and the *boxes* rep-

resent exons, which are enlarged for clarity. UTR refers to untranslated regions of the transcripts. Translated regions are exons 2–10

The Molecular Basis of GHI

GHR Gene Mutations

The GHR gene (Fig. 2.2) is on the proximal short arm of chromosome 5, spanning 86 kilobase pairs. The 5' untranslated region (UTR) is followed by 9 coding exons. Exon 2 encodes the last 11 base pairs of the 5'-UTR sequence, an 18 amino acid signal sequence, and the initial 5 amino acids of the extracellular hormone-binding domain. Exons 3–7 encode the extracellular hormone-binding domain, except for the terminal 3 amino acids of this domain, which are encoded by exon 8. Exon 8 further encodes the 24 amino acid hydrophobic transmembrane domain and the initial 4 amino acids of the intracellular domain. Exons 9 and 10 encode the large intracellular domain. Exon 10 also encodes the 2 kb 3'-UTR [3].

More than 50 mutations in the GHR have been described in the approximately 250 known patients with GHR deficiency (Laron syndrome), which result in a clinical picture identical to that of severe GH deficiency, but with elevated serum GH concentrations. The report of the characterization of the complete GHR gene included the first description of a genetic defect of the GHR, a deletion of exons 3, 5, and 6 [3]; recognition that the exon 3 deletion represented an alternatively spliced variant without functional significance resolved the dilemma of explaining deletion of nonconsecutive exons. In addition to the original exon 5 and 6 deletion, another deletion of exon 5

has been described, along with numerous nonsense mutations, missense mutations, frameshift mutations, splice mutations, and a unique intronic mutation resulting in insertion of a pseudo-exon. A number of other mutations have been described that are either polymorphisms or have not occurred in the homozygous or compound heterozygous state [1].

All but a few of the defects result in absent or extremely low levels of GH-binding protein (GHBP). Noteworthy is the D152H missense mutation that affects the dimerization site, thus permitting the production of the extracellular domain in normal quantities but failure of dimerization at the cell surface, which is necessary for signal transduction and IGF-I production. Two defects that are close to (G223G) or within (R274T) the transmembrane domain result in extremely high levels of GHBP. These defects interfere with the normal splicing of exon 8, which encodes the transmembrane domain, with the mature GHR transcript being translated into a truncated protein that retains GH-binding activity but cannot be anchored to the cell surface.

All these homozygous and compound heterozygous defects, whether involving the extracellular domain or the transmembrane domain and whether associated with very low or unmeasurable GHBP, or with the more rare transmembrane defects that can be associated with elevated GHBP levels, result in a typical phenotype of severe GH deficiency (Table 2.2). In contrast, the intronic mutation present in the heterozygous state in a mother and daughter with

Table 2.2 Clinical features of severe IGF-I deficiency due to GH deficiency or GH receptor deficiency or STAT5b mutation

Growth
<ul style="list-style-type: none"> • Birth weight—normal; birth length—usually normal • Growth failure, from birth, with velocity ½ normal • Height deviation correlates with (low) serum levels of IGF-I, IGF-II, and IGFBP-3 • Delayed bone age but advanced for height age • Small hands or feet
Craniofacial characteristics
<ul style="list-style-type: none"> • Sparse hair before age 7; frontotemporal hairline recession all ages • Prominent forehead • Head size more normal than stature with impression of large head • “Setting sun sign” (sclera visible above iris at rest) 25% <10 years of age • Hypoplastic nasal bridge, shallow orbits • Decreased vertical dimension of face • Blue scleras • Prolonged retention of primary dentition with decay; normal permanent teeth may be crowded; absent 3rd molars • Sculpted chin • Unilateral ptosis, facial asymmetry (15%)
Musculoskeletal/body composition
<ul style="list-style-type: none"> • Hypomuscularity with delay in walking • Avascular necrosis of femoral head (25%) • High-pitched voices in all children, most adults • Thin, prematurely aged skin • Limited elbow extensibility after 5 years of age • Children underweight to normal for height, most adults overweight for height; markedly decreased ratio of lean mass to fat mass, compared to normal, at all ages • Osteopenia indicated by DEXA
Metabolic
<ul style="list-style-type: none"> • Hypoglycemia (fasting) • Increased cholesterol and LDL-C • Decreased sweating
Sexual development
<ul style="list-style-type: none"> • Small penis in childhood; normal growth with adolescence • Delayed puberty • Normal reproduction

relatively mild growth failure (both with standard deviation score [SDS] for height -3.6), and resulting in a dominant negative effect on GHR formation, is not associated with other phenotypic features of GH deficiency [12]. This splice mutation preceding exon 9 results in an extensively attenuated, virtually absent intracellular domain. Japanese siblings and their mother have a similar heterozygous point mutation of the donor splice

site in intron 9, also resulting in mild growth failure compared to GHR deficiency but with definite, although mild, phenotypic features of GH deficiency [13]. GHBP levels in the Caucasian patients were at the upper limit of normal with a radiolabeled GH-binding assay and in Japanese patients twice the upper limit of normal, using a ligand immunofunction assay. These heterozygous GHR mutants transfected into permanent cell lines have demonstrated increased affinity for GH compared to the wild-type full-length GHR, with markedly increased production of GHBP. When co-transfected with full-length GHR, a dominant negative effect results from overexpression of the mutant GHR and inhibition of GH-induced tyrosine phosphorylation and transcription activation [14]. Naturally occurring truncated isoforms have also shown this dominant negative effect in vitro [15].

A novel intronic point mutation was discovered in a highly consanguineous family with two pairs of affected cousins with GHBP-positive GH insensitivity and severe short stature, but without the facial features of severe GH deficiency or insensitivity. This mutation resulted in a 108-bp insertion of a pseudo-exon between exons 6 and 7, predicting an in-frame, 36-residue amino acid sequence, in a region critically involved in receptor dimerization [16].

Genetic Disorders Affecting GH-GHR Signal Transduction and Transcription

STAT5b

There are seven members of the STAT family of proteins activated by multiple growth factors and cytokines, participating in a wide range of biological activities, particularly relating to growth and immunocompetence. While GH activates four members of this family, STAT5b has emerged as the one that is crucial for growth [17]. The GH-activated GHR recruits the STAT5b which docks to specific phosphotyrosine residues on the receptor, undergoing tyrosine phosphorylation by the receptor-associated JAK2. The phosphorylated STAT dissociates rapidly from the receptor, forms a dimer,

and translocates to the nucleus, binding to DNA, interacts with other nuclear factors, and initiates transcription.

Ten patients have been described with seven autosomal recessively transmitted mutations of *STAT5b* [18]. Similar to children with severe GH deficiency and GHR deficiency, but unlike those with IGF-I gene or IGF-I receptor mutations (below), birth size is normal, indicating GH-independent IGF-I production in utero. Also similar to GH and GHR deficiency, postnatal growth shows rapid decline in SDS ranging from -9.9 to -5.6 at diagnosis, which was from 2.1 to 31 years of age. Serum concentrations of IGF-I, IGFBP-3, and ALS were markedly low; basal and stimulated GH concentrations were either normal or elevated. The features (growth patterns, facial disproportion, and biochemistry with the exception of GH-binding protein) have been identical to those of patients with severe GHR deficiency.

As might be expected because *STAT5b* is involved in intracellular signaling for other cytokine receptors besides the GHR, immunodeficiency with serious complications has been described in all but one of the reported patients with *STAT5b* mutation. Reported abnormalities include T cell functional defects, low numbers of NK and $\gamma\delta$ T-cells, and IL-2 signaling defects.

PTPN11

Fifty percent of children with Noonan syndrome, which is characterized by short stature, cardiac defects, skeletal abnormalities, and facial dysmorphism, have been found to carry a gain of function mutation of *PTPN11*. This gene encodes a non-receptor-type tyrosine phosphatase (SHP-2) involved in intracellular signaling for a variety of growth factors and cytokines. Activated SHP-2 is thought to serve as a negative regulator of GH signaling. Children with Noonan syndrome who have this mutation have more severe statural deficit than those without the mutation. They also have lower serum concentrations of IGF-I and IGFBP-3 with higher GH concentrations and less robust growth response to rhGH treatment, all suggesting mild GH insensitivity [17].

Mutations of the IGF-I Gene

Failure of IGF-I synthesis due to a gene deletion was described in a patient with a homozygous partial deletion of the IGF-I gene [19]. His profound intrauterine growth failure (IUGR) persisted into adolescence and he had sensorineural deafness with severe mental retardation and micrognathia. Subsequently, a second patient was described with the same clinical phenotype but a different mutation also resulting in near absence of circulating IGF-I [20]. A third similarly affected patient had a defect in IGF-I synthesis resulting in production of a nonfunctioning IGF-I molecule circulating in high concentration [21].

The absence of the craniofacial phenotype of severe GH or GHR deficiency and the presence of normal IGFBP-3 in these patients, despite absent IGF-I function, indicate that the craniofacial features and low IGFBP-3 of GH and GHR deficiency are related to an absence of the direct effects of GH that do not act through the medium of IGF-I synthesis. It is also noteworthy that profound IUGR and mental retardation are not characteristic of GH or GHR deficiency, but IGF-I knockout mice have defective neurological development as well as growth failure. Thus, IGF-I production in utero does not appear to be GH-GHR dependent.

A milder molecular defect in IGF-I synthesis due to a homozygous missense mutation of the IGF-I gene has been described, resulting in IUGR and postnatal growth failure, undetectable IGF-I by highly specific monoclonal assay but elevated levels with a polyclonal assay, microcephaly, and mild intellectual impairment, but with normal hearing [22].

Mutations of the Acid-Labile Subunit Gene

ALS is an 85-kDa glycoprotein that modulates IGF-I bioavailability by stabilizing the binary complex of IGF-I and IGFBP-3. It is a member of a family of leucine-rich repeat (LRR) proteins that are able to participate in protein-protein interactions; $\sim 75\%$ of the mature protein corresponds to the consensus motif for the LRR super-

family. ALS is a donut-shaped molecule that binds readily to the binary complex of IGF-I and IGFBP-3, but does not interact directly with free IGF-I and has low affinity for IGFBP-3 that is not bound to IGF-I. Functional mutation of the ALS gene was first reported in 2004 and by 2010 included 21 individuals from 16 families, with 16 discrete homozygous or compound heterozygous mutations noted [23–29]. ALS is undetectable and serum IGF-I and IGFBP-3 concentrations are extremely low. Nonetheless, statural impairment is generally modest, with near adult or adult height, available for 11 of the patients, being better than target height in one patient, less than 1 SD below mean in an adopted child with unknown target height, and within 1.5 SD of target height in 6 others. The modest, at worst, effect on growth despite circulating concentrations of IGF-I that are similar to those of severe GH insensitivity or deficiency emphasizes the compensatory capability of local IGF-I production [30].

Mutations of the IGF-I Receptor

Mouse studies demonstrated that deletion of the IGF-I receptor resulted in intrauterine growth retardation and perinatal death. Thus, it is not surprising that only heterozygous mutations in the IGF-I receptor gene (*IGF-IR*) have been described. The initial report of *IGF-IR* mutation followed systematic examination in two groups of children with intrauterine growth retardation (IUGR) who remained greater than 2 SD below normal for length after 18 months of age. This population was selected for study because IGF-I receptor knockout mice have more severe IUGR than do IGF-I knockout mice. Among 42 US subjects who did not have low IGF-I and IGFBP3 concentrations, a single patient was identified with compound heterozygosity for mutations of the IGF-I receptor resulting in amino acid substitutions. She had severe IUGR (birth weight 1,420 g at 38 weeks), poor postnatal growth, and elevated concentrations of IGF-I and integrated GH concentration when prepubertal, consistent with IGF-I resistance. The location of the mutations was within a putative ligand-binding domain

and the heterozygous parents were subnormal in stature and also had low birth weight. In the same study, a European group of 50 IUGR subjects was selected who had elevated circulating IGF-I concentrations and a second subject identified, who had a heterozygous nonsense mutation reducing the number of IGF-I receptors on fibroblasts; two other affected first-degree relatives were identified [31]. In all, 17 cases in 7 families, each family with a unique mutation, had been described by 2010, with in vitro confirmation of failure of IGF-I binding and function [31–36].

There is wide phenotypic variability among these individuals, with height SDS ranging from –1.6 to –5.7, substantial delay in osseous maturation to normal bone ages for chronologic age and normal timing of puberty, and normal to markedly increased serum concentrations of IGF-I and IGFBP3. The effect of IGF-I gene mutations on intrauterine growth, however, is uniformly replicated in this less severe circumstance.

Epidemiology

Race/Nationality

Among the approximately 250 affected individuals identified worldwide with growth failure due to GHR mutations, about two-thirds are Semitic and half of the rest are of Mediterranean or South Asian origin. The Semitic group includes Arabs, Oriental, or Middle Eastern Jews, and the largest group, the genetically homogeneous 90+ conversos in Ecuador (Jews who converted to Christianity during the Inquisition). The identification of an Israeli patient of Moroccan origin with the E180 splice mutation found in the Ecuadorian patients indicated the Iberian provenance of this mutation, which readily recombined in the isolated communities of these sixteenth-century immigrants established in the southern Ecuadorian Andes. Recently, additional patients with the E180 splice mutation on the same genetic background have been identified in Chile and Brazil, likely of the same origin. Among those who are not of Semitic, South Asian, or Mediterranean origin,

there is wide ethnic representation, including Northern European, Eurasian, East Asian, African, and Anglo-Saxon (Bahamas) [9].

The individuals with STAT5b mutation include Kuwaiti siblings, two unrelated Argentinians, siblings from Brazil, one patient from Turkey, and one patient from the Caribbean [17].

ALS mutations were reported in three Kurdish brothers, three unrelated and two sibling Spanish patients, three Norwegian/German siblings, two unrelated Swedish patients, and individual patients of Turkish, Argentinian, Ashkenazi Jewish, Pakistani, mixed European, and Mayan origin. Families with heterozygous mutations of the IGF-I receptor were of Dagestani, European, and Japanese origin [23–29].

IGF-I receptor mutations have been reported from the USA, Germany, Russia, Korea, Japan, and the Netherlands [31–36].

Gender

Among patients observed since the original description of the GHR deficiency syndrome by Laron, Pertzalan, and Mannheimer in 1966 [37] until 1990, a normal sex ratio was noted. The initial report of 20 cases from a single province in Ecuador included only one male [38], but subsequent observations from an adjacent province indicated a normal sex ratio, and a few more males were subsequently identified in the initial province [39]. The abnormal sex ratio for that locus remains unexplained. All but 3 of the 21 individuals with *IGFALS* mutations are male, but this may reflect ascertainment bias because of the relatively modest effects on stature being of less concern in girls than in boys.

Morbidity and Mortality

The only available report of the effect of GHR deficiency on mortality comes from the Ecuadorian population [39]. Because families in the relatively small area from which the Ecuadorian patients originate had intensive experience with this condition, lay diagnosis was considered reliable. Of

79 affected individuals for whom information could be obtained, 15 (19%) died under 7 years of age, as opposed to 21 out of 216 of their unaffected siblings (9.7%, $p < 0.05$). The kinds of illnesses resulting in death, such as pneumonia, diarrhea, and meningitis, were no different for affected than for unaffected siblings.

The complete lifespan included in the Ecuadorian cohort provided an opportunity to look at adult mortality risk factors. Twenty-three adults with GHD had elevated cholesterol levels, normal HDL-cholesterol levels, elevated LDL-cholesterol levels, and normal triglyceride concentrations compared to relatives and nonrelated community controls. It was postulated that the effect of IGF-I deficiency due to GHRD was to decrease hepatic clearance of LDL-C, because the triglyceride and HDL-C levels were unaffected. This effect was independent of obesity or of IGFBP-1 levels, which were used as a surrogate for insulinemia. The key pathogenic factor was thought to be the absence of GH induction of LDL receptors in the liver [40]. Preliminary data suggest an increased cardiovascular mortality in the Ecuadorian GHR-deficient adult subjects. In contrast, there has been no death recorded from cancer, despite a high cancer mortality in relatives [41].

Clinical Findings (Table 2.2)

Growth

Individuals with GHI due to GHR deficiency usually have normal intrauterine growth [42]. Nonetheless, IGF-I is required for normal intrauterine growth as demonstrated by patients with IUGR with a proven IGF-I gene defect or IGF receptor mutation. Thus, this intrauterine IGF-I synthesis does not appear to be GH dependent.

SDS for length declines rapidly after birth in GHR deficiency (Fig. 2.3) indicating the GH dependency of extrauterine growth. Growth velocity with severe GH deficiency or GHR deficiency is approximately half normal (Fig. 2.4). Occasional periods of normal growth velocity may be related to improved nutrition.

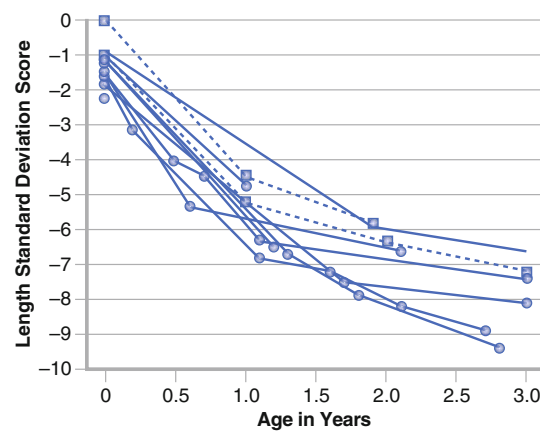


Fig. 2.3 Length standard deviation scores of nine girls from Ecuador (open circles, solid lines) and two brothers from southern Russia (solid circles, dashed lines) with known birth lengths, followed over the first 2–3 years of life [Adapted from *Trends Endocrinol Metab*, vol 5, #7, Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG, Pollock BH. Growth in growth hormone insensitivity, pp 296–303, Copyright 1994, with permission from Elsevier]

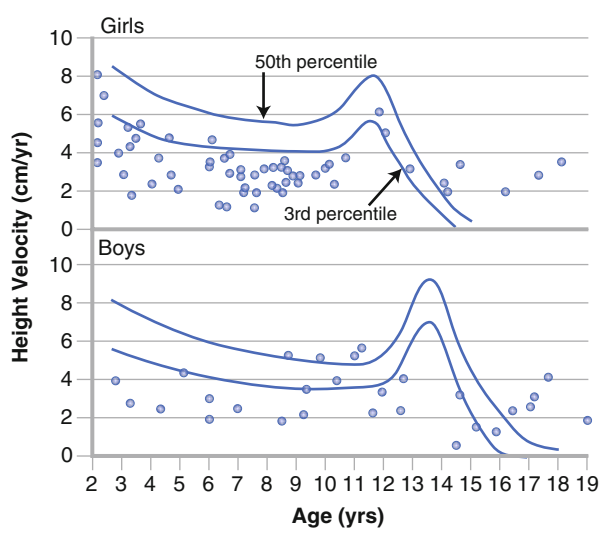


Fig. 2.4 Growth velocities of 30 Ecuadorian patients (10 males) with GH receptor deficiency; repeated measures were at least 6 months apart. Third and 50th percentiles are from Tanner JM, Davies PSW: Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr* 1985; 107:317–329 [Adapted from *Trends Endocrinol Metab*, vol 5, #7, Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG, Pollock BH. Growth in growth hormone insensitivity, pp 296–303, Copyright 1994, with permission from Elsevier]

Despite normal sexual maturation, the pubertal growth spurt is minimal or absent in GHR deficiency, as documented in the most extensive available data, from Israel and Ecuador [42, 43]. The adolescent growth spurt is GH dependent, reflected in significantly elevated circulating lev-

els of GH and IGF-I compared to preadolescence and adulthood [44].

Adult stature in GHR deficiency varies from –12 to –5.3 SDS in Ecuadorian patients and –9 to –3.8 SDS in others in the literature, using the US standards [42]. This is a height range of

95 cm to 124 cm for women and 106–141 cm for men in the Ecuadorian population. This wide variation in the effect of GHR deficiency on stature was not only seen within the population but also within affected families; such intrafamilial variability has also been described with severe GH deficiency due to GH gene deletion [10].

Some patients with GHR deficiency may have an appetite problem in addition to their IGF-I deficiency. Crosnier et al. [45] studied a child aged 3½ years with GHR deficiency who had severe anorexia. With his usual intake of approximately 500 kcal/day, he grew at a rate of 2 cm/year. With moderate hyperalimentation to approximately 1,300 kcal/day, growth rate increased to 9 cm/year without significant change in plasma IGF-I level. The hyperalimentation period was associated with an increase in the IGFBP-3 bands on Western ligand blots, from total absence in the anorexic period to levels comparable to those seen in GH deficiency. The catch-up growth noted could not be explained by hyperinsulinism, which has provided the explanation for accelerated or normal growth in children with GH deficiency and obesity following removal of a craniopharyngioma. There was no appreciable increase in circulating basal or stimulated insulin during the hyperalimentation. In this patient, there was speculation that a nutrition-dependent autocrine/paracrine increase in IGF-I concentration at the cartilage growth plate might have occurred, independent of the GHR. The importance of adequate nutrition for catch-up growth was emphasized by this study, which also reinforced the notion that normal periods of growth in patients with GHR deficiency without IGF-I replacement therapy, as noted in Fig. 2.4, might be explained by periods of improved nutrition alone.

Craniofacial Characteristics

Children with GHR deficiency are recognized by knowledgeable family members at birth because of craniofacial characteristics of frontal prominence, depressed nasal bridge, and

sparse hair, as well as small hands or feet and hypoplastic fingernails. Decreased vertical dimension of the face is demonstrable by computer analysis of the relationships between facial landmarks and is present in all patients when compared with their relatives including those without obviously abnormal facies [46]. Blue scleras, the result of decreased thickness of the scleral connective tissue, permitting visualization of the underlying choroid, were originally described in the Ecuadorian population and subsequently recognized in other populations with GHR deficiency as well as in severe GH deficiency [38, 47]. Unilateral ptosis and facial asymmetry may reflect positional deformity due to decreased muscular activity in utero, although mothers do not recognize decreased fetal movement in pregnancies with affected infants [48].

As noted above, individuals with STAT5b mutations have growth impairment and facial dysmorphism indistinguishable from those with homozygous or compound heterozygous GHR mutation. IGF-I mutations result in micrognathia and microcephaly but no craniofacial abnormalities similar to those with GHR or STAT5b mutations.

Musculoskeletal and Body Composition

Hypomuscularity is apparent in radiographs of infants with GHR deficiency and is thought to be responsible for delayed walking, despite normal intelligence and timing of speech onset [48]. Radiographs of the children also suggest osteopenia; dual-photon absorptiometry and dual-energy X-ray absorptiometry in children and adults confirm this. A study of dynamic bone histomorphometry in adults with GHR deficiency, however, demonstrated normal bone volume and formation rate, with the only abnormality being reduction in trabecular connectivity. This study suggested that some of the densitometry findings were artifactual, due to the small bone size [49].

Limited elbow extensibility seen in most patients over 5 years of age in the Ecuadorian

population is an acquired characteristic, absent in younger children and increasing in severity with age [38, 48]. That this feature is not peculiar to the Ecuadorian population or to IGF-I deficiency due to GHR deficiency has been confirmed by finding a Brazilian patient having a different GHR mutation with limited elbow extension [50] and observing this finding in all but the youngest patient in a family with eight individuals affected by multiple pituitary deficiencies [47]. The cause of this elbow contracture is unknown.

Although children appear overweight, they are actually underweight to normal weight for height, while most adults, especially females, are overweight with markedly decreased lean to fat ratios [48].

Reproduction

GHR deficiency is associated with small penis size with normal penile growth at adolescence or with testosterone treatment in childhood. Although puberty may be delayed 3–7 years in some 50% of individuals, there is normal adult sexual function with documented reproduction by males and females [39]. Females require C-section delivery.

Intellectual and Social Development

GHR Deficiency

Intellectual impairment was originally considered a feature of the Laron syndrome on the basis of uncontrolled observations [51]. Among 18 affected children and adolescents tested with the Wechsler Intelligence Scale for Children, only 3 had IQs within the average range [90–110]; of the remaining 15 subjects, 3 were in the low average range [80–89], 3 in the borderline range [70–79], and 9 in the intellectually disabled range [<70]. These studies were done without family controls, so that the possibility of other factors related to consanguinity that might affect intellectual development and the appropriateness of the testing materials in this

Middle Eastern population could not be addressed. In a follow-up study 25 years later, the investigators reexamined 8 of the original 18 patients and 4 new patients with GHR deficiency, excluding 5 patients with mental disabilities who were in the original study [52]. This group had mean verbal and performance IQs of 86 and 92 on the Wechsler scale without evidence of visual motor integration difficulties that had been noted in the earlier group, but there was a suggestion of deficient short-term memory and attention. The investigators hypothesized that early and prolonged IGF deficiency might impair normal development of the central nervous system or that hypoglycemia common in younger patients may have had a deleterious effect.

Sporadic anecdotal reports of patients with GHR deficiency suggested a normal range of intelligence. The collective data from the European IGF-I treatment study group, which includes a wider range of clinical abnormality than either the Ecuadorian or Israeli population, notes a mental retardation rate of 13.5% among 82 patients, but formal testing was not carried out [53]. Here again, the high rate of consanguinity was proposed as a possible explanation; hypoglycemia could not be correlated with these findings.

In the Ecuadorian population, exceptional school performance was reported among 51 affected individuals of school age or older who had attended school, with 44 typically in the top 3 places in their classes and most thought to be as bright or brighter than the smartest of their unaffected siblings [54].

The first controlled documentation of intellectual function in a population with GHR deficiency was in the Ecuadorian patients, a study of school-age individuals compared to their close relatives and to community controls. No significant differences in intellectual ability could be detected among these groups, using nonverbal tests with minimal cultural limitations. It was hypothesized that the exceptional school performance in this population might have been related to the lack of social opportunities due to extreme short stature, permitting

greater devotion to studies and superior achievement in school for IQ level [55].

STAT5b Gene Mutation

Consistent with other evidence that the IGF-I dependence for intrauterine brain development is independent of the need for an intact GH activation pathway, individuals with STAT5b mutations do not have impaired brain development.

IGF-I Gene Mutation

There was marked intellectual impairment in the patients with severe IGF-I deficiency due to mutation of the IGF-I gene, indicative of the dependence of intrauterine brain development, as well as intrauterine growth, on IGF-I. That this intrauterine IGF-I production is not dependent on GH is suggested by the intellectual normality with severe GH and GHR deficiency, consistent with gene disruption studies in mice. The IGF-I-deleted mouse is neurologically impaired, while the GHR-deficient mouse is behaviorally normal [56, 57]. Thus, GH-dependent IGF-I production is not necessary for normal brain development and function.

IGF-I Receptor Mutation

The effect of heterozygous IGF-I receptor mutation on head growth and brain development is less impressive than with IGF-I gene defects. Small head size was recorded frequently, including in a proband with above-average IQ and her daughter with slight motor delay at 1½ years of age. Except for one individual with a reported IQ of 60, intellectual development of the other probands ranged from normal to mild retardation [31–36].

IGFALS Mutation

Normal neurological development with *IGFALS* mutation would be expected, consistent with normal brain development in children with severe GH or GHR deficiency who would not be stimulating intrauterine synthesis of ALS. This would imply that the GH-independent IGF-I production necessary for normal intrauterine somatic and brain growth is local (paracrine/autocrine) rather than endocrine.

Biochemical Features

Growth Hormone

Affected children with GHR deficiency have random GH levels that are greater than 10 ng/ml and may be as high as 200 ng/ml, with enhanced responsiveness to stimulation and paradoxical elevations following oral and intravenous glucose, as is seen in acromegaly [58]. The GH levels show normal diurnal fluctuation [7]. Twenty-four-hour profiles demonstrate marked GH variability among adult patients with suppression by exogenous recombinant human IGF-I [7]. Thus, the normal sensitivity of the GH secretion is preserved, despite lifelong elevated GH levels and lack of feedback suppression from IGF-I.

Postpubertal patients with GHR deficiency may have normal or elevated basal levels of GH but invariably demonstrate hyperresponsiveness to stimulation, which is all the more impressive considering their obesity, which suppresses GH responses in normal individuals. In the Ecuadorian population, mean basal GH level in adults was significantly lower than that in children (11 ± 11 ng/ml versus 32 ± 22 ng/ml, $p < 0.0001$). This is thought to be related to the greater, though still markedly abnormal, IGF-I levels in the adults, resulting in some feedback inhibition of GH secretion [7, 48].

ALS mutations are associated with normal GH levels, despite very low circulating IGF-I concentrations. IGF-I receptor deficiency, which is an IGF-I-resistant state, rather than GH-resistant state, can also be associated with normal GH levels.

Growth Hormone-Binding Protein

Absence of GHBP in the circulation was initially considered a requirement for the diagnosis of GHR deficiency, along with the clinical phenotype, very low concentrations of IGF-I and IGFBP-3, and elevated (in children) or normal to elevated (in adults) GH levels. Chromatographic

analysis for serum GHBP, however, showed measurable though reduced levels in a number of patients. The ligand-mediated immunofunction assay (LIFA) used to measure GHBP serum levels since 1990 uses an anti-GH monoclonal antibody to measure the amount of GH bound to GHBP. As a largely functional assay, this should not detect structurally abnormal though expressed GHBP.

As noted above, certain genetic defects in the GHR, those affecting dimerization or anchoring of the GHBP to the cell membrane and dominant negative mutations of the cytoplasmic domain, can result in normal or markedly elevated GHBP levels. In the Ecuadorian population, despite in vitro evidence for failure of production of normally spliced receptor, 4 children and 4 adults out of 49 patients had serum GHBP levels higher than 40% of the sex-specific lower limit for controls, and one adult male had a level in the lower portion of the normal adult male range. The presence or amount of GHBP measured did not relate to stature [48]. There were no age-dependent changes, indicating that the difference in IGF values between children and adults was not related to the GHBP levels and the GHBP levels did not correlate with stature or with serum IGF-I levels. Although finding of extremely low or undetectable levels of GHBP serves as an important diagnostic feature, it is not a sine qua non for the diagnosis of GHR deficiency.

Insulin-Like Growth Factors

The lowest serum levels of IGF-I are seen in severe congenital defects in GH synthesis (GH gene deletion, GHRH-R deficiency), with deletion of the IGF-I gene and with GHR deficiency. IGF-II is not as severely suppressed, its reduction likely related to diminution of GHBP-3 rather than to decreased synthesis. In chronic disease states associated with acquired GHI, IGF-I levels are more likely to be reduced than are concentrations of IGF-II and IGFBP-3.

Among 50 Ecuadorian patients homozygous for the E180 splice-site mutation, IGF-I levels were significantly greater in adults 16–67 years

of age ($n=31$, 25 ± 19 mcg/L) than in the 19 subjects under 16 years of age (3 ± 2 mcg/L, $p<0.0001$), although still markedly below the normal range of 96–270 mcg/L. The children's levels were too low to correlate with stature, but in the adults, IGF-I levels correlated inversely with statural SDS with a coefficient of 0.64 ($p<0.001$). IGF-II levels in adults were also significantly greater than in children (151 ± 75 mcg/L versus 70 ± 42 mcg/L, normal 388–792 mcg/L, $p<0.0001$). The correlation between serum IGF-I and IGF-II levels was highly significant, $r=0.53$, $p<0.001$. With no indication of age difference in GHBP levels, the increased levels of IGF-I and IGF-II with adulthood suggests effects on synthesis of these growth factors which are not mediated through the GHR and initially thought to be under the influence of sex steroids. This hypothesis was challenged by findings in patients with GHRH resistance due to mutation of the GHRH receptor. Sexually mature individuals with GHRH receptor mutation and affected children have comparably very low IGF-I (and IGFBP-3) serum concentrations [59]. The correlation of IGF-I levels with stature in adults with GHR deficiency indicates that, despite the markedly low levels, the influence of IGF-I on stature remains important in these subjects.

IGF-Binding Proteins

In IGF deficiency states that are the result of GH or GHR deficiency, IGFBP-3 is reduced, and as noted above, in children and adults with GHR deficiency, this reduction correlates with statural impairment [42]. In renal disease, elevated IGFBP-3 and IGFBP-1 and IGFBP-2 are thought to impair the delivery of normal levels of IGF-I [11].

Short-term and extended treatment of GHI with IGF-I has failed to result in increases in IGFBP-3 [7, 60–64], whereas treatment of GHD with recombinant human GH restores levels to normal. This indicates that IGFBP-3 production is under the direct influence of GH.

IGFBP-1 is elevated in GH and GHR deficiency; in GHR deficiency, it is the most abundant IGFBP

and is strongly inversely related to insulinemia. IGFBP-2 is present at a mean 300% of control concentrations in children with GHR deficiency and 175% of control in affected adults, a significant difference. The IGFBP-3 levels in adults with GHR deficiency are significantly greater than those in affected children [65].

Diagnostic Issues in GH Insensitivity

GHI due to deficiency is readily diagnosed in its typical and complete form because of severe growth failure, the somatic phenotype of severe GH deficiency, elevated serum GH levels, and marked reduction in IGF-I, IGF-II, and IGFBP-3 concentrations, with increased concentrations of IGFBP-1 and IGFBP-2. Most such individuals will also have absent to very low concentrations of GHBP, although the less common GHBP-positive forms make absence of GHBP an important but not essential criterion. As noted in Table 2.1, some of the biochemical features of GHR deficiency may be shared by conditions associated with acquired GH insensitivity, such as malnutrition and liver disease.

The demonstration of a homozygous mutation or a compound heterozygous mutation affecting the GHR usually provides definitive diagnosis. Thirty-one of the 82 patients reported by Woods et al. [53] had a genetic study of the GHR, of whom 27 had abnormalities affecting both alleles of the GHR gene, in association with clinically and biochemically unequivocal GHR deficiency. Identification of heterozygous mutations, however, is not necessarily helpful because, as noted earlier, polymorphisms have been described which appear to have no phenotypic consequences.

Partial GH Resistance

GH resistance might be expected to occur in an incomplete form, analogous to insulin resistance, androgen insensitivity, or thyroid hormone resistance. Affected children might have growth failure with normal or slightly increased GH

secretion, variable but usually decreased GHBP levels, and decreased IGF-I concentrations, but not as severely reduced as in GH or GHR deficiency, and might respond to supraphysiologic doses of GH. It might also be expected, given the need for dimerization of the GHR for signal transduction, that certain mutations could have a dominant negative effect in the heterozygous state.

Credibility for a heterozygous defect as a cause of short stature requires the demonstration of functional significance, not only by transfection of the mutant allele, but by cotransfection with wild-type GHR gene, to approximate the circumstance *in vivo*. Goddard et al. [66] identified six mutations in eight children with short stature (SDS for height -5.1 to -2.0) and normal or increased stimulated GH levels. One patient had compound heterozygosity involving a novel mutation in exon 4 (E44K) and a mutation in exon 6 previously associated with GHR deficiency in the homozygous state (R161C). Two other patients were heterozygous for this mutation. The other five patients included two who were heterozygous for the same novel mutation in exon 7 (R211H) and one each with novel mutations of exon 5 (C122X), exons 7 (E224D), and exon 10 (A478T). Expression *in vitro* of these four novel mutations involving the extracellular domain has shown functional effects, although cotransfection studies have not been reported. The defect involving exon 10 has not been expressed *in vitro*. Other defects without demonstrable significance have been described involving exon 10. None of these putative partial GHI patients had the clinical phenotype of GH deficiency. Five of the eight patients were treated with GH with variable improvement in growth velocity, from slight to dramatic, in the first year. This variable response is typical of that seen with recombinant GH treatment of idiopathic short stature (ISS).

The subjects studied by Goddard et al. [66] were selected from the large Genentech National Cooperative Growth Study database in pursuit of the question raised by the observation that GHBP concentrations are low in children with ISS, that is, short children without a recognizable syndrome

or GH deficiency. Using a ligand-mediated immunofunction assay, Carlsson et al. [67] studied a large number of short children with known causes of growth failure such as GH deficiency and Turner syndrome, or ISS, and compared their GHBP concentrations in serum to those of normal controls. Ninety percent of the children with ISS had GHBP concentrations below the control mean and nearly 20% had concentrations that were 2 standard deviations or more below the normal mean for age and sex. In a further analysis of the ISS group in this database, Attie et al. [68] identified over 500 patients who had been treated with rhGH and had normal GH stimulation tests, of whom, as noted above, 20% had low GHBP concentrations. While those with the low GHBP levels had significantly lower IGF-I concentrations and higher mean 12-h serum GH levels, the GH differences were numerically unimpressive ($2.8 \mu\text{g/L} \pm 1.1$ versus 2.3 ± 1.1). Particularly relevant to the supposed GH resistance, there was no correlation of GHBP levels with the growth response to exogenous GH in these patients. The search for defects in the GHR to explain ISS in the 100 subjects with low GHBP yielded 7 heterozygous mutations, but in studies of the families of these children, short stature did not segregate with the heterozygous state.

More recently, the Genentech database was analyzed for evidence of GH insensitivity among ~5,000 patients entered between 1993 and 1996, with short stature (height standard deviation score < -2) being treated with GH. Over 40% were deemed IGF-I deficient, and half of these to have the novel diagnosis of “primary IGF-I deficiency,” that is, normal GH responses with low IGF-I. The ISS group as a whole had a similar growth response to GH as did GH-deficient patients during the first year of treatment, with growth response correlating inversely with IGF-I baseline levels, exactly the opposite of the correlation that would be expected if they had GH insensitivity [69]. This evidence of GH sensitivity in the presence of low IGF-I concentrations is consistent with the observation that the growth response to rhGH in children with ISS who have low levels of IGF-I is greater than in those with more normal levels [70] and with the lack of

correlation of growth response to GH in ISS relative to peak stimulated GH levels.

What cannot be appreciated from such a cross-sectional analysis of data from hundreds of pediatric endocrinologists is the clinical context in which the biochemical measures were obtained. Decreased circulating IGF-I with normal or elevated GH levels occurs with chronic illness and undernutrition. Many of the children seen with what is termed ISS are poor eaters with decreased body mass index and may be receiving treatment for hyperactivity which can suppress appetite and growth. Even acutely, IGF-I levels decline substantially with fasting, which is considered a means of protecting against potential insulin-like effects on glycemia. Clinical investigations of children with ISS and varying responses to GH stimulation tests or IGF-I generation tests (in which GH is given for several days to stimulate IGF-I synthesis) have indicated that GH insensitivity is, at most, an uncommon finding [71]. Nonetheless, promotional efforts and clinical investigations have been based on the hypotheses that much, if not most, ISS was due to IGF-I deficiency as the result of GH insensitivity and that exogenous IGF-I was appropriate growth-promoting therapy [71]. These hypotheses were not data based and disproven by the manufacturers’ clinical trial data in which subjects had dubious IGF-I deficiency, normal GH sensitivity, and responses to rhIGF-I in relation to bone age advance which were no different than in control untreated subjects [72, 73].

The possibility of an effect of heterozygosity for a mutation which causes GHR deficiency in the homozygous state was explored in the unique Ecuadorian cohort with a single mutation, permitting genotyping of numerous first-degree relatives. There was a minor difference in stature between carrier and homozygous normal relatives, and no difference in IGF-I or IGFBP-3 concentrations, indicating minimal, if any, influence of heterozygosity for the E180 splice mutation of the GHR [74]. A more general indication of the lack of influence of heterozygosity for GHR mutations involving the extracellular domain on growth comes from studies of the large multicenter European-based GHI study [53].

In both the European and Ecuadorian populations, the stature of parents and of unaffected siblings does not correlate with statural deviation of affected individuals, while expected high correlation exists between parents and unaffected offspring. If the mutations that cause growth failure in the homozygous state also affected growth in heterozygotes, heterozygous parents and predominantly heterozygous siblings would have height SDS values which correlated with those of affected family members. In the Ecuadorian families, there was no difference in height correlations with parents between carriers and homozygous normal offspring.

Treatment

Soon after the cloning of the human IGF-I cDNA, human IGF-I was synthesized by recombinant DNA techniques (rhIGF-I) and physiologic studies undertaken with intravenously administered rhIGF-I [75]. Subcutaneous preparations of rhIGF-I became available in 1990.

GHR Deficiency

During administration of rhIGF-I at a dose of 40 $\mu\text{g/kg}$ sc every 12 h over 7 days to 6 Ecuadorian adults with GHR deficiency, hypoglycemia was avoided by having the subjects eat meals after the injections [7]. Elevated 24-h GH levels typical of the condition were rapidly suppressed, as was clonidine-stimulated GH release. Mean peak serum IGF-I levels were 253 ± 11 ng/ml reached between 2 and 6 h after injection and mean trough levels were 137 ± 8 ng/ml before the next injection, values not different from those of normal control Ecuadorian adults. Although IGFBP-3 levels did not increase, elevated baseline IGFBP-2 levels (153% of control) increased 45% ($p < 0.01$). The short-term studies demonstrated that there was an insignificant risk of hypoglycemia despite low levels of IGFBP-3. There remained, however, concern whether the low IGFBP-3 levels would result in more rapid clearance of IGF-I, with blunting of the therapeutic effect.

The initial report of treatment for longer than 10 months was in 2 children with GHR deficiency who had height velocities of 4.3 and 3.8 cm/year at 8.4 and 6.8 years of age. Their elevated serum GH levels were suppressed and serum procollagen-I levels increased shortly after starting treatment; 6-month height velocities increased to 7.8 and 8.4 cm/year, but in the second 6 months of treatment, the velocities decreased to 6.6 and 6.3 cm/year and in the subsequent 5 months returned to pretreatment values. These patients were treated with a dose of 40 mcg/kg subcutaneously twice daily (bid) and the waning of their growth response after a year suggested that this dosage was not adequate for sustained effect [76].

The first IGF-I treatment report from the large Ecuadorian cohort was of growth and body composition changes in two adolescent patients treated with a combination of IGF-I (120 mcg/kg bid) and long-acting gonadotropin-releasing hormone analog to forestall puberty. A girl aged 18 and boy aged 17 years, with bone ages of 13½ and 13 years, experienced an approximate tripling of growth velocity, increased bone mineral density, and maturation of facial features with rhIGF-I treatment for 1 year. There was initial hair loss followed by recovery of denser and curly hair with filling of the frontotemporal baldness, the appearance of axillary sweating, loss of deciduous teeth, and appearance of permanent dentition. They had coarsening of their facial features. Submaxillary gland enlargement was noted in one patient and fading of premature facial wrinkles in the other patient. Serum IGF-I levels increased into the normal range for age during the 2–8 h following IGF-I sc injection [77]. Studies were done at doses of 40, 80, and 120 mcg/kg with pharmacokinetic profiles suggesting a plateau effect between 80 and 120 mcg/kg per dose. It was considered that the carrying capacity of the IGFBPs was saturated at this level. Mean serum IGF-II levels decreased concurrently with the increase in IGF-I, and serum IGFBP-3 levels did not respond to prolonged IGF-I treatment. There was no apparent change in the half-life of IGF-I during the treatment period, indicating no alteration of IGF-I pharmacokinetics induced by prolonged treatment.

Table 2.3 Treatment with rhIGF-I for 1–2 years of children with GH insensitivity

	Europe [64]	Ecuador [63]		Israel [78]	International [79]
Number	26 ^a	7	15	9	56 ^b
Age (years)	3.7–19.6	3.1–15.2	4.7–17.1	0.5–14.6	1.7–17.5
Dose (/kg)	40–120 µg bid	80 µg bid	120 µg bid	150–200 µg/d	60–125 µg bid
<i>Ht velocity—cm/year (SD)</i>					
Pre-Rx	N/A	3.0 (1.8)	3.4 (1.4)	4.7 (1.3)	2.8 (1.8)
Year 1	8.8 (1.9) ^c	9.1 (2.2)	8.8 (1.1)	8.2 (0.8)	8.0 (2.2)
Year 2	7 (1.4) ^c	5.6 (2.1)	6.4 (1.1)	6.0 (1.3) ^d	5.8 (1.5) ^e
<i>Height SDS (SD)</i>					
Pre-Rx	−6.5 (13) ^c	−8.0 (1.8)	−8.5 (1.3)	−5.6 (1.5)	−6.7 (1.8)
Year 1	−5.8 (1.5) ^c	−7.2 (1.8)	−7.5 (1.1)	−5.2 (1.7)	−5.9 (1.8)
Year 2	−5.4 (1.8) ^c	−6.7 (1.4)	−7.0 (1.2)	−5.8 (1.2) ^d	−5.6 (1.8) ^e

^aIncludes 2 patients with GH-neutralizing antibodies^bIncludes 8 patients with GH-neutralizing antibodies^cFor 15 subjects treated for 4 years^dFor 6 of the 9 subjects^e48 subjects

Seventeen prepubertal Ecuadorian patients were entered into a randomized double-blind, placebo-controlled trial of IGF-I at 120 mcg/kg sc bid for 6 months, following which all subjects received IGF-I. Such a study was considered necessary because of the observation of spontaneous periods of normal growth in these youngsters, the suggestion that nutritional changes that might accompany intervention would be an independent variable, and the need to control for side effects, particularly hypoglycemia, which occur in the untreated state. The nine placebo-treated patients had a modest but not significant increase in height velocity from 2.8 ± 0.3 to 4.4 ± 0.7 cm/year, entirely attributable to three individuals with 6-month velocities of 6.6–8 cm/year. Although this response was attributed to improved nutritional status, there was no accompanying increase in IGFBP-3 as noted with nutrition-induced catch-up growth in the French GHR-deficient patient with anorexia [45]. For those receiving IGF-I, the height velocity increased from 2.9 ± 0.6 to 8.8 ± 0.6 cm/year and all 16 patients had accelerated velocities during the second 6-month period when all were receiving IGF-I. No changes or differences in circulating IGFBP-3 concentrations were noted. There was no difference in the rate of hypoglycemia

events, nausea or vomiting, headaches, or pain at the injection site between the placebo and IGF-I-treated groups. Initial hair loss occurred in 90% of subjects, similar to what is seen with treatment of hypothyroidism, reflecting more rapid turnover [62].

In the 2-year treatment study comparing 120 mg/kg bid dosage to 80 mg/kg bid treatment of GHR deficiency in Ecuadorian patients, no differences in growth velocity or changes in height SDS, height age, or bone age between the two dosage groups (Table 2.3). A group of six subjects receiving the higher dose followed for a third year continued to maintain second-year growth velocities. The annual changes in height age in both the first and the second year of treatment correlated with IGF-I trough levels which tended to be in the low normal range despite a failure of serum IGFBP3 levels to increase (Fig. 2.5). The comparable growth responses to the two dosage levels and the similar IGF-I trough levels confirmed the plateau effect at or below 80 mcg/kg body weight twice daily observed in the first two patients [63, 77].

The Israeli report of 3 years' treatment of nine patients is the only one in which patients were given IGF-I as a single daily dosage (150–200 µg/kg) [78]. The European study group noted height

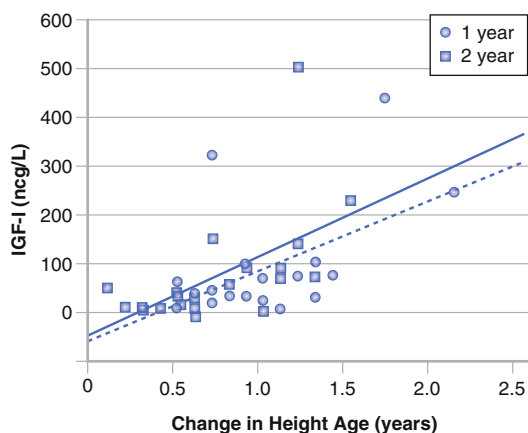


Fig. 2.5 Correlation of annual changes in height age and differences between baseline and trough levels of serum IGF-I with rhIGF-I treatment in 22 children with GHRD. The *dashed line* represents the 1-year correlation ($r=0.54$, $p=0.009$) and the *solid line* represents the 2-year correlation ($r=0.58$, $p=0.005$) [Adapted from The Journal of Endocrinology and Metabolism, Two year treatment of growth hormone receptor deficiency (GHRD) with recombinant insulin-like growth factor-I in 22 children: Comparison of two dosage levels and to GH treated GH deficiency. 82 (2), February 1997, pp 629–633. Copyright 1997, The Endocrine Society]

SDS improvement of 0.7 over 1 year and 1.2 over 2 years [64], and the Ecuadorian patients had an improvement of 1 SDS over 1 year and 1.5 over 2 years at the higher dose and 0.8 SDS over 1 year and 1.3 SDS over 2 years at the dosage of 80 mcg/kg twice daily. The Israeli patients had an improvement in height SDS of only 0.4 over 1 year and for the six patients with 2-year data, 0.2 over 1 year and 0.4 over 2 years. The kinetic studies that originally formed the rationale for twice-daily administration were supported by these observations.

The collective experience of treating the rare conditions in which responsiveness to GH is severely impaired includes approximately 150 individuals, mostly with GHR deficiency, and fewer than 10% with GH inactivating antibodies (Table 2.3). The growth velocity increment in the first year was 4.3 cm in the European and mecasermin (Genentech/Tercica) study populations [79] and 5.6 cm in the Ecuadorian population, all groups receiving comparable doses of rhIGF-I administered twice daily. In the Israeli population

given a single injection of a comparable total daily dose, the increment was only 3.6 cm/year. Height SDS improvement in the first year of treatment paralleled these increments at 0.7, 0.8, and 0.6 for the twice-daily rhIGF-I in the European, Ecuadorian, and International-mecasermin groups, respectively, and 0.2 for the Israeli population. The stimulatory effect on growth wanes rapidly after the first year, with only modest continued improvement. Among 76 patients treated for a mean 4.4 years, overall height SDS improvement was 1.4, almost all of which was achieved in the first 2 years of treatment [79].

Comparison of the growth response of 22 rhIGF-I-treated GHR deficiency patients and 11 GH-treated GH-deficient patients in the same setting demonstrated mean growth velocity increment in those with GHR deficiency to be 63% of that achieved with GH treatment of GH deficiency in the first year and less than 50% in the second and third years (Table 2.3). The inadequate growth response compared to GH treatment of GH deficiency persisted over this extended treatment period, with a mean improvement in height SDS of only 1.4, from -5.6 to -4.2 , thus only sustaining the improvement of the first 2 years of treatment, as noted in Table 2.3. The importance of GH effects beyond hepatic IGF-I, IGFBP-3, and ALS synthesis is confirmed by this experience with attempted IGF-I replacement therapy in which only endocrine IGF-I can be replaced [8]. Near-total deletion of the GHR in liver only in the mouse model had no effect on total body or bone linear growth [80].

Limitations of Endocrine IGF-I Replacement

The observation that growth failure due to GH insensitivity cannot be adequately corrected with endocrine IGF-I replacement is not explained by concomitant IGFBP3 deficiency. Substantial tissue delivery is reflected in profound effects on adipose tissue, facies, and lymphoid tissue in treated patients (see below). This indicates that twice-daily injection provides

more than adequate replacement of endocrine IGF-I, despite both IGFBP-3 and ALS deficiency which are not corrected by IGF-I treatment. The maintenance of circulating levels of IGF-I despite severe IGFBP-3 and ALS deficiency may be the result of binding to other IGFBPs; IGFBP-2 is elevated in GHR deficiency and increases further with rhIGF-I therapy [7].

If the tissue dose of IGF-I in patients with GHI treated with IGF-I is supraphysiologic, as indicated by increases in body fat and acromegaloid facial changes, why then do we not see sustained growth acceleration as in GH-treated GH deficiency? The dual-effector hypothesis remains the best explanation for inadequate growth response [8]. With diminished ability to stimulate prechondrocyte differentiation and local IGF-I production, children with GHI can expect only partial recovery of normal growth with IGF-I replacement. Thus, IGF-I replacement therapy of GI may need to continue longer than GH treatment of GH deficiency to achieve more normal height. This goal will likely require suppressing adolescence in most children with GHI, using GnRH analogs [77].

In addition to statural attainment, goals of replacement therapy with IGF-I in GHI include improvement in body composition, normalization of facial appearance, and possible reduction of risk factors for childhood and adult mortality. All studies that have monitored body composition have verified lean mass increases, including increased bone density. Unlike GH replacement therapy, however, which restores normal lipolysis, IGF-I therapy is lipotrophic, increasing or sustaining the high-percentage body fat. Normalization of craniofacial features has also been apparent [81]. Voice change has not been remarked on but can be expected.

The reduction of risk factors for the higher mortality in infancy and childhood with GHR deficiency is to be expected with IGF-I therapy, but the reason for this increased risk is unknown. Leukocytes share in the general upregulation of IGF-I receptors in GHR deficiency and appear to function normally in this condition [82]. In a study of one affected infant (who died at 7 months with bronchitis) and five adults with GHR

deficiency from Ecuador, Diamond et al. [83] demonstrated a variety of immune disturbances in the infant and three of the adults. The pathologic significance of these findings remains uncertain [84].

Purported Partial GHI

The definition adopted by the FDA for “severe primary IGFD” was height SDS < -3 , basal IGF-I SDS < -3 , and normal or elevated GH concentration. Growth velocity, osseous maturation, or projected height relative to mean parental stature, factors that are important in clinical evaluation of short children, were not considered. Younger children may have quite low values for IGF-I that are not diagnostically useful, and at any age, a single measurement may vary considerably from a subsequent determination. There is also inconsistency between laboratories, and normal ranges vary widely. In one analysis, three of four laboratories failed to identify 15–20% of Ecuadorian patients with molecularly proven GHRD using the FDA criterion for IGF-I concentration < -3 SD. Values may be spuriously low as a result of high susceptibility of IGF-I to post sampling proteolysis [71]. Children, especially boys, with constitutional delay in growth and maturation (CDGM), who do not have biochemical markers of undernutrition, may be hypermetabolic and have mean IGF-I concentrations that are only 40% of those of normal age-mates, which could lead to an inappropriate diagnosis of IGFD [85]. This interpretation may be artifactual because of comparison to norms for chronologic age rather than biologic (bone) age.

Further insight into the wide variability in IGF-I concentrations in the absence of endocrine deficiency comes from a study comparing African and Italian children of comparable height but with the African children having significantly lower weight and BMI and mean IGF-I and IGFBP-3 levels $< 1/3$ those of the Italian children [86]. Wide fluctuations in IGF-I concentrations can be seen in normal prepubertal children, including levels < 2 SDS [87]. Finally, IGF-I generation tests have poor reproducibility [88].

The off-label promotion of rhIGF-I has been based on two considerations which are not evidence based: that many children with ISS have partial GH insensitivity and that appropriate therapy for these individuals is recombinant IGF-I. The absence of convincing evidence for this hypothesis, the limited ability of endocrine IGF-I to restore normal growth in those with unequivocal GH unresponsiveness, the suppression of local GH effects on growth with IGF-I administration, the risk profile, and the absence of data on efficacy in other than proven severe GH insensitivity led the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society to conclude that rhIGF-I use is only justified in conditions approved by the US Food and Drug Administration (FDA) and that use for growth promotion in other children should only be investigational [89]. The manufacturer of IGF-I “estimates that approximately 30,000 children in the US are affected by primary IGFD, which is also similar to the estimated [European Union] EU market size” [71]. Considering that fewer than 200 children with GH insensitivity due to GHRD, transduction defects, or GH-inhibiting antibodies had been identified worldwide in the previous 20 years, it is apparent that there was exuberant anticipation and extensive promotion of off-label use. Indeed, current clinical trials demonstrate the loosening of criteria from those in the approval by FDA [www.clinicaltrials.gov].

In January 2008, Tercica announced that they had begun dosing the first patient in a phase II clinical trial evaluating the combination of GH and IGF-I in a study that was scheduled for completion at the end of 2011 to involve 100 subjects over 5 years of age. This is a four-arm study involving rhGH alone in a dose of 45 $\mu\text{g/kg}$ daily and the same dose of GH with once-daily injections of either 50, 100, or 150 $\mu\text{g/kg}$ IGF-I. Inclusion requires height SDS ≤ -2 (which is less stringent than the criterion of SDS ≤ -2.25 for GH treatment of ISS) and IGF-I SDS ≤ 1 , along with normal response to GH stimulation testing, and bone age ≤ 11 years for boys and ≤ 9 years for girls. There are no growth velocity criteria. This study was likely to include a substantial number of children, especially males, with CDGM, the most common explanation for short stature in the

growth clinic, and other normal short children. It is noteworthy that there was not an IGF-I monotherapy arm and that the IGF-I was given as a single daily injection in contrast to the pharmacokinetic studies and clinical experience with this drug.

There is no reason to expect better growth response with IGF-I in patients who do not have proven insensitivity to GH than with recombinant GH, based on the absence of evidence of GH resistance as a cause of their short stature. In fact, monotherapy with IGF-I in individuals who have normal or even somewhat reduced GH production and action should result in suppression of endogenous GH, which occurs rapidly with rhIGF-I administration in both normal and GHRD subjects [7]. This GH suppression will reduce IGFBP-3 and ALS production and, most importantly, decrease GH delivery to growing bone, with reduction of chondrocyte proliferation and autocrine/paracrine IGF-I production, potentially decreasing growth velocity.

Data presented by the manufacturer of mecasermin in 2009 provided evidence that countered the notion that “primary IGFD” due to partial GHI was a valid diagnosis. In their clinical trial of individuals carrying this supposed diagnosis, supra-physiologic doses of IGF-I were required, resulting in circulating IGF-I levels of +2 SDS, to obtain a growth effect; thus, a pharmacologic rather than physiologic replacement therapy was required, which would be inconsistent with replacement therapy for primary IGFD. Also inconsistent with the diagnosis of primary IGFD were the normal baseline growth velocities in these subjects. When these subjects underwent IGF-I generation tests (administration of GH for 5 days), there was a 76.5% increase in mean IGF-I level and 34% increase in mean IGFBP-3 concentration [90]. Both of these are approximately 50% greater responses than in normals and indicative of better than normal GH sensitivity.

Safety Concerns with Recombinant IGF-I

Episodes of hypoglycemia which may be severe are common in infants and children with GHR deficiency. In contrast to the far less common

hypoglycemia of GH deficiency which is corrected by GH replacement therapy, IGF-I treatment increases the risk of hypoglycemia in children with GHR deficiency. Hypoglycemia has been the most common early adverse event, reported in 49% of subjects in the largest series, including 5% with seizures [79]. In the 6-month, placebo-controlled Ecuadorian study, hypoglycemia was reported in 67% of individuals receiving placebo and 86% of those treated with rhIGF-I, an insignificant difference [62]. Finger-stick blood glucose measurements in 23 subjects residing at a research unit indicated frequent hypoglycemia before breakfast and lunch, which did not increase in frequency with rhIGF-I administration [79]. Five of the subjects participated in a crossover, placebo-controlled study for 6 months with a 3-month washout period with fasting glucose determinations performed three times daily by caregivers for the entire 15-month study. The percentage of glucose values <50 mg/dL was 2.6% with placebo and 5.5% with rhIGF-I, not a significant difference. In practice, hypoglycemia associated with IGF-I treatment appears reasonably controllable by adequate food intake.

Pain at the injection site is common. Injection site lipohypertrophy is frequent, affecting at least one-third of subjects; this is the result of failure to rotate injections and injection into the lumps, which can attenuate growth response. The inotropic effect of IGF-I results in asymptomatic tachycardia in all treated patients, which clears after several months of continued use [91]. Benign intracranial hypertension or papilledema has been noted in approximately 5% of IGF-treated subjects. While headache is frequent, the placebo-controlled study found no difference in incidence between those receiving placebo injections and those receiving IGF-I. Parotid swelling and facial nerve palsy have been described. Lymphoid tissue hypertrophy occurs in over 25% of patients, with hypoacusis, snoring, and tonsillar/adenoidal hypertrophy that required surgical intervention in over 10% of patients. Thymic hypertrophy was noted in 35% of subjects having regular chest radiographs. It is worth noting that some of these side effects may be more frequent than reported because they take time to develop; for example,

snoring incidence in the first year for the 25 longest treated subjects in the mecasermin study was only 4% but increased to 65% for the entire study period [79].

Anti-IGF-I antibodies have developed in approximately half of the IGF-I-treated patients during the first year of treatment, but these have had no effect on response [78, 79]. Urticaria has been noted in subjects participating in the trial of IGF-I with GH. Transient elevation of liver enzymes has also been noted [78].

Coarsening of facial features with disproportionate growth of the jaw reminiscent of acromegaly has been common, particularly among those of pubertal age [77]. In contrast to the increase in lean body mass and decreasing percentage of body fat that occurs with GH treatment of GHD, both lean and fat mass increase with rhIGF-I therapy [75]. Mean body mass index (BMI) increased from +0.6 SDS to +1.8 SDS during 4–7 years of treatment with rhIGF-I in the European multicenter trial, and severe obesity has occasionally occurred [92]. BMI measurement may not accurately reflect the degree of obesity, which can be a doubling or tripling of body fat as demonstrated by dual-energy X-ray absorptiometry [93]. Hyperandrogenism with oligomenorrhea or amenorrhea, acne, and elevated serum androgens has been described in prepubertal and young adult patients given single daily injections of rhIGF-I [94]. There have been two instances of anaphylaxis from rhIGF-I treatment [73].

It is not known whether there might be long-term mitogenic effects of extended therapy with rhIGF-I in growing children. The role of IGF-I in carcinogenesis, as an antiapoptotic agent favoring the survival of precancerous cells, together with the increased cancer risk in hypersomatotropic states, and the evidence for aberrant tissue effects in rhIGF-I-treated patients dictate a need for long-term follow-up of rhIGF-I-treated patients [95].

GH Therapy

Five individuals with IGF-I receptor mutations have been treated with recombinant GH with four

having substantial improvements in growth velocity but without the impressive catch-up growth seen with GH treatment of GH deficiency; the exception was an individual who had no response over 6 months of trial. The patient with partial primary deficiency of IGF-I responded to supraphysiologic doses of recombinant GH with catch-up growth [22].

Conclusions

Genetic causes of GHI from the GHR to IGF-I action remain rare, but their identification has greatly enhanced understanding of growth processes and introduced challenging questions, for example, about phenotypic variability between genetic defects at various sites with comparable biochemical effects and among individuals with the same or similar mutations of a particular gene. Acquired GHI is relatively common as a complication of a variety of chronic problems associated with growth failure. Treatment of the genetic causes of GHI remains inadequate because of the inability of exogenous rhIGF-I to replicate GH effects at the growth plate.

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