### DEFINITION AND CLASSIFICATION

Growth hormone insensitivity (GHI) 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 1 lists the known conditions associated with GH resistance and their clinical and biochemical features. Only GH receptor (GH-R) deficiency (GHRD) and GH-GHR signal transduction defects are appropriately described as primary GH resistance or insensitivity. Inability to generate insulin-like growth factor-I (IGF-I) resulting from mutation of the IGF-I gene (2) and resistance to IGF-I due to mutation of the IGF-I receptor (3) are properly considered primary IGF-I deficiency and IGF-I resistance.

The conditions that have been associated with secondary or acquired GHI do not consistently demonstrate elevated serum GH concentrations, low levels of IGF-I, or even 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; such patients have extremely low or unmeasurable serum concentrations of GH (4). Growth failure associated with chronic renal disease is thought to be
<table>
<thead>
<tr>
<th>Condition</th>
<th>Growth Failure</th>
<th>GH deficiency phenotype</th>
<th>GH</th>
<th>GHRP</th>
<th>IGF-I</th>
<th>IGFBP-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I gene deletion</td>
<td>severe (with IUGR)</td>
<td>no</td>
<td>increased</td>
<td>normal</td>
<td>absent</td>
<td>normal</td>
</tr>
<tr>
<td>IGF-I receptor deficiency</td>
<td>severe (with IUGR)</td>
<td>no</td>
<td>increased</td>
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<td>normal</td>
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<td>Primary GH insensitivity</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>GHR deficiency/autosomal recessive forms</td>
<td>severe</td>
<td>yes</td>
<td>increased (child) normal/elevated</td>
<td>absent/low/normal</td>
<td>markedly decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>GHR deficiency/dominant negative forms</td>
<td>moderate</td>
<td>no or mild</td>
<td>elevated</td>
<td>2 × normal</td>
<td>marked decrease</td>
<td>low normal</td>
</tr>
<tr>
<td>GH–GHR signal transduction defect</td>
<td>severe (Arab)</td>
<td>yes (Arab)</td>
<td>elevated</td>
<td>normal</td>
<td>marked decrease</td>
<td>normal (Arab)</td>
</tr>
<tr>
<td>Acquired GH insensitivity</td>
<td>moderate (Pakistani)</td>
<td>no (Pakistani)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>GH inhibiting antibodies</td>
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<td>yes</td>
<td>absent</td>
<td>normal</td>
<td>marked</td>
<td>decreased</td>
</tr>
<tr>
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<td>increased</td>
<td>decreased</td>
<td>variable normal or</td>
<td></td>
</tr>
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<td>increased</td>
<td>decreased</td>
<td>decreased increased</td>
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<tr>
<td>Renal disease</td>
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<td>no</td>
<td>normal</td>
<td>decreased</td>
<td>normal</td>
<td>increased</td>
</tr>
</tbody>
</table>
related to increased concentrations of IGF binding proteins (IGFBP) with normal or elevated GH and usually normal total IGF-I levels \(^{(5)}\). Malnutrition and other catabolic states that have been associated with GHI may be teleologically similar to the nonthyroidal illness (sick euthyroid) syndrome \(^{(6)}\).

### THE GH-IGF-I AXIS

GH synthesis and secretion by the anterior pituitary somatotrophs is under the control of stimulatory GH releasing hormone (GHRH) and inhibitory somatostatin (SST) from the hypothalamus (Fig. 1). The stimulation and suppression of GHRH and SST result from a variety of neurologic, metabolic, and hormonal influences. Of particular importance to discussions of GHI is the feedback stimulation of SST by IGF-I, with resultant inhibition of GH release \(^{(1,7)}\).

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 \(^{(8)}\). GHBP is the proteolytic cleavage product of the full-length membrane bound receptor molecule in humans \(^{(9)}\). This characteristic permits the assay of circu-
lating GHBP as a measure of cellular bound GHR, which usually correlates with GHR function (2,10).

The GH molecule binds to a molecule of cell surface GHR at a unique binding site, which then dimerizes with another GHR molecule at a second binding site in the extracellular domain, so that a single GH molecule is enveloped by two GHR molecules (11). 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). Other effector proteins have also been examined in various systems. This is a mechanism typical of the growth hormone/prolactin/cytokine receptor family that includes receptors for erythropoietin, interleukins, and other growth factors (8).

The effect of GH on growth is indirect, via stimulation of IGF-I production, primarily in the liver (12). Hepatic 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 (13). IGFBP-3 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 IGFBP-3 are produced in the liver as a direct effect of GH. The remainder of bound IGF is in a 50-kD complex largely with IGFBP-1 and IGFBP-2. IGFBP-1 production is highly variable, with the highest concentrations in the fasting, hypoinsulinemic 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 therapy of such patients (7,14).

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. IGFBPs 1, 2, 4, and 6 inhibit IGF action by preventing binding of IGF-I with its specific receptor. The binding of IGFBP-3 to cell surfaces is thought to decrease its affinity for IGF-I, effectively delivering the IGF-I to the type 1 IGF receptor. IGFBP-5 potentiates the effects of IGF-I in a variety of cells; its binding to extracellular matrix proteins allows fixation of IGFs and enhances IGF binding to hydroxyapatite. IGFs stored in such a manner in soft tissue may enhance wound healing. IGF independent mechanisms for IGFBP-1 and IGFBP-3 proliferative effects have been demonstrated in vitro and nuclear localization of IGFBP-3 has been reported. Cell surface association and phosphorylation of IGFBP determine the influence of IGFBPs. Specific protease activity, particularly affecting IGFBP-3, is also important in the modulation of IGF action in target tissues. IGFBP-3 specific proteolytic activity may alter the affinity of the binding protein for IGF-I, resulting in release of free IGF-I for binding to the IGF-I receptor (7,12).

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, stimulating clonal expansion and maturation of the chondrocytes, with growth. It is estimated that approximately 20% of GH stimulated growth results from this autocrine-paracrine IGF-I mechanism (15).
DISCOVERY OF LARON SYNDROME AND PRE-MOLECULAR STUDY

Following the initial report (16) of three Yemenite Jewish siblings, “with hypoglyce-
mia and other clinical and laboratory signs of growth hormone deficiency, but with
abnormally high concentrations of immunoreactive serum growth hormone,” 22 patients
were reported from Israel, all Oriental Jews, with an apparent autosomal recessive mode
of transmission in consanguineous families (17). These reports preceded the recognition
of the critical role of cell surface receptors in hormone action and it was postulated that
the defect was in the GH molecule that these patients produced. This impression was
substantiated by the observation of free-fatty acid mobilization, nitrogen retention, and
growth in patients being administered exogenous GH (16,17). These effects may have
been due to other pituitary hormones in the crude extracts administered or to nutritional
changes in the investigative setting.

In the first patient reported outside of Israel, in 1968, there was no response to exog-
enous GH, leading to the hypothesis that the defect was in the GH receptor (18). This
hypothesis was substantiated by the failure to demonstrate sulfation factor activation
(subsequently identified as IGF-I) with exogenous GH administration, reported in 1969
(19) and reports in 1973 and 1976 that the patients’ GH was normal on fractionation,
normal in its binding to antibodies, and normal in its binding to hepatic cell membranes
from normal individuals (20–23). In vitro demonstration of cellular unresponsiveness to
GH was demonstrated by the failure of erythroid progenitor cells from the peripheral
blood of two patients to respond to exogenous GH (24). The failure of radioiodine
labelled GH to bind to liver cell microsomes obtained from biopsy of two patients with
Laron syndrome confirmed that the defect was in the GHR (25).

Just before the report that human circulating GHBP was the extracellular domain of
the cell surface GHR (9), two reports appeared indicating that GHBP was absent from
serum of patients with Laron syndrome (26,27).

THE MOLECULAR BASIS OF GHI

The GHR Gene

The GHR gene 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 his
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 (10).

GHR Gene Mutations

The initial report of the characterization of the GHR gene described non-contiguous
deletion of exons 3, 5, and 6 in two Israeli patients with Laron syndrome (28). The
deletion of exon 3 has subsequently been shown to be an alternatively spliced polymor-
phism, rather than a functional component of the defect (29). Only four Israeli patients
have been described as homozygous for this mutation and a fifth was heterozygous (with,
Part I / Rosenbloom

apparently, a different mutation of the other allele), among over 30 Oriental Jewish patients in Israel, indicating heterogeneity for the genetic defect in the GHR within an ethnically homogeneous population (30). No other exon deletions have been described in patients with GHI, but 38 additional defects of the GHR gene have been described in association with GHI, including 8 nonsense mutations, 14 missense mutations, 5 frame shift mutations, 10 splice mutations, and a unique intronic mutation resulting in insertion of a pseudo-exon (10,31). The functional insignificance of exon 3 is emphasized by the fact that no mutations affecting this exon have been associated with GHI. Neither have functional mutations been described in exon 2. A number of other mutations have been described which are either polymorphisms or have not occurred in the homozygous or compound heterozygous state (30).

Only 3 of the homozygous or compound heterozygous defects that have been described thus far do not result in the expected absent or extremely low levels of GHBP. The D152H missense mutation occurs at the GHR dimerization site, with normal production and GH binding of the extracellular domain, but failure to dimerize at the cell surface. Thus, despite failure of GHR function, circulating concentrations of GHBP are normal. High concentrations of GHBP in serum occur with the splice mutations that are close to (G223G) or within (R274T) the transmembrane domain. These defects interfere with the normal splicing of exon 8, which encodes the transmembrane domain; the mature GHR transcript is translated into a truncated protein that retains GH binding activity but cannot be anchored to the cell surface (30).

Several heterozygous mutations of the GHR have been proposed as causative of moderate growth failure with absence of other clinical characteristics of GHI (32–35), but the heterozygous effects of only two cytoplasmic domain defects have been supported by biochemical findings and in vitro experimentation. A Caucasian mother and daughter and Japanese siblings and their mother with moderate short stature were heterozygous for an intronic splice mutation preceding exon 9 and a point mutation of the donor splice site in intron 9 of the GHR gene, respectively, resulting in an extensively attenuated, virtually absent intracellular domain (36,37). Individuals with these heterozygous defects produce both normal and abnormal GHR protein, giving three possible types of GHR dimerization: a fully functional unit formed from two normal GHR molecules, a heterodimer of unknown functional capacity comprised of a mutant and normal molecule, or a nonfunctional homodimer formed by two mutant GHR molecules lacking a cytoplasmic domain. The normal function of some of these dimers was demonstrated in the affected Japanese mother and her two children by a substantial increase in the subnormal IGF-I levels following 3 d of GH injection (37).

When these heterozygote GHR mutants were transfected into permanent cell lines, they demonstrated increased affinity for GH compared to the wild-type full-length GHR and markedly increased the production of GHBP. A dominant negative effect occurred when the mutant was co-transfected with full-length GHR, the result of overexpression of the mutant GHR and inhibition of GH-induced tyrosine phosphorylation and transcription activation (36,38). Naturally occurring truncated isoforms have also shown this dominant negative effect in vitro (39–41).

There is no convincing clinical or experimental evidence for any mutation involving the extracellular or transmembrane domains of the GHR having a deleterious effect in the heterozygous state, either as an isolated occurrence, or in the carrier relatives of individuals with GHI (7,32,33,42–44).
In the largest cohort of GHI due to GHRD, that from Ecuador comprising 71 patients, all but one subject have the E180 splice mutation, which is shared with at least one Israeli patient of Moroccan heritage (45). Only four of the other reported defects are not family- or ethnicity-specific. The R43X mutation, two other nonsense mutations (C38X, R217X), and the intron 4 splice mutation have been described in disparate populations, on different genetic backgrounds, indicating that these are mutational hotspots (30).

A novel intronic point mutation was recently described in a highly consanguineous family with two pairs of affected cousins with GHBP-positive GHI. This mutation resulted in a 108 bp insertion of a pseudoxon between exons 6 and 7, predicting an in-frame, 36 residue amino acid sequence. This is a region critically involved in receptor dimerization (31).

Mutation of the GHR has been identified in fewer than half of the patients with GHRD outside of Ecuador; thus, it is likely that the list of mutations will continue to grow and provide further insight into the function of the GHR.

**GH-GHR Signal Transduction Abnormality**

The full clinical picture of Laron syndrome, with elevated circulating concentrations of GH, was seen in Arab siblings with apparently normal binding of GH to the GHR, inferred from normal serum concentrations of GHBP and IGFBP-3 (46). A failure of GH-GHR signal transduction was also been proposed to explain short stature in four GHBP positive children from two unrelated Pakistani families (47). The Pakistani patients differed from the Arab children in having low serum concentrations of IGFBP-3. In one family, there were severe and typical phenotypic features of GH deficiency, and the defect was thought to be close to the GHR, preventing activation of both the STAT and MAPK pathways demonstrated in cultured fibroblasts. In the other family, there was a less marked phenotype and a defect in activation of MAPK, but not the STAT pathway in cultured fibroblasts from the patients (48).

**EPIDEMIOLOGY**

*Geographic and Ethnic Distribution*

Ethnic origin is known for over 90% of the ~260 reported cases of GHRD; it is likely that an equal number are not reported (30). Nearly 50% are Oriental Jews as described in the original reports (15,16), or known descendants of Iberian Jews who converted to Catholicism during the Spanish Inquisition. The latter comprise the largest (n = 71) and only genetically homogenous patient group. The finding of a Jewish patient of Moroccan origin with the same mutation as the Ecuadorian patients supports the hypothesis that this mutation was brought to the New World by Spanish conversos (new Christians) fleeing the Inquisition (45). Thus far, there is no explanation for the middle eastern predominance of this condition, although the high frequency of consanguinity in Arab and traditional Jewish populations is certainly a factor. Nearly 90% of patients are either Oriental Jews, Arabs, or other middle easterners, from elsewhere in the Mediterranean area, or from the Indian subcontinent. Many of those from other parts of the world may have middle eastern Semitic origins. The small numbers of non-Semitic, non-Mediterranean, non-Indian patients include a genetic isolate of Anglo-Saxons from a Bahamian island, five Africans, five Japanese, two siblings from Cambodia, a Vietnamese, and several from northern Europe (10).
**Morbidity and Mortality**

The only available report of the effect of GHRD on mortality comes from the Ecuadorian population (49). 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 yr 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. This is of interest because GHD in adults is associated with premature atherosclerosis and increased cardiovascular mortality, with GH replacement therapy improving the risk factors of hyperlipidemia and obesity (50). Twenty-three adults with GHD had elevated cholesterol levels, normal HDL-cholesterol (HDL-C) levels, elevated LDL-cholesterol (HDL-C) levels, and normal triglycerides compared to relatives and non-related community controls. It was postulated that the effect of IGF-I deficiency due to GHRD was to decrease hepatic clearance of LDL-C, since the triglyceride and HDL-C levels were unaffected. This effect was independent of obesity or IGFBP-1 levels, which were used as a surrogate for insulinemia (50). The key pathogenic factor was thought to be the absence of GH induction of LDL receptors in the liver (51).

Of 8 Ecuadorian patients over 50 yr of age followed for greater than 7 yr, 2 died of heart disease, an uncommon problem in the Andean setting (48). This might suggest comparable increased cardiovascular risk to that seen with GHD in adults.

**CLINICAL FINDINGS (TABLE 2)**

**Growth**

Many, if not most, patients with GHI due to GHRD have normal intrauterine growth (1). Children with GH gene deletion also have normal intrauterine growth despite total absence of endogenous GH (4). Nonetheless, IGF-I is required for normal intrauterine growth as demonstrated by patients with intrauterine growth retardation with a proven IGF-I gene defect (2) or IGF receptor mutation (3). Thus, this intrauterine IGF-I synthesis does not appear to be GH dependent.

Standard deviation score (SDS) for length declines rapidly after birth (Fig. 2) indicating the GH dependency of extra-uterine growth. Growth velocity with severe GHD or GHI is approximately half normal (Fig. 3). Occasional periods of normal growth velocity may be related to improved nutrition.

Despite normal sexual maturation, the pubertal growth spurt is minimal or absent, as documented in the most extensive available data, from Israel and Ecuador (1,53). The adolescent growth spurt is GH dependent, reflected in significantly elevated circulating levels of GH and IGF-I compared to preadolescence and adulthood (54). Among 24 Israeli patients followed from infancy to adulthood, persistent growth beyond the normal time of adolescence was seen only in boys. In the Ecuadorian population, girls also showed this phenomenon (Fig. 3). Adult stature in GHRD 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 (1). This is a height range of 95–124 cm for women and 106–141 cm for men.
Chapter 2 / GH Insensitivity

Fig. 2. 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 yr of life. Reprinted from *Trends Endocrinol Metab*, vol 5, Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG, Pollock BH. Growth in growth hormone insensitivity, pp 296–303, 1994, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.

Fig. 3. Growth velocities of 30 Ecuadorian patients (10 males) with GH receptor deficiency; repeated measures were at least 6 mo 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;107:317–328. Reprinted from *Trends Endocrinol Metab*, vol 5, Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG, Pollock BH. Growth in growth hormone insensitivity, pp 296–303, 1994, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.
in the Ecuadorian population. This wide variation in the effect of GHRD on stature was not only seen within the population but also within affected families, and this intrafamilial variability has also been described with severe GHD due to GH gene deletion (4).

Some patients with GHRD may have an appetite problem in addition to their IGF-I deficiency. Crosnier et al. (55) studied a child aged 3 1/2 yr with GHRD who had severe anorexia. With his usual intake of approx 500 kcal/d, he grew at a rate of 2 cm/yr. With moderate hyperalimentation to approx 1300 kcal/d, growth rate increased to 9 cm/yr 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 GHD. The catch-up growth noted could not be explained by hyperinsulinism, which has provided the explanation for accelerated or normal growth in children with GHD 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. Not considered at the time was the possibility that IGFBP-3 itself might have growth promoting effects. The importance of adequate nutrition for catch-up growth was emphasized by this study, reinforcing the notion that normal periods of growth in patients with GHRD without IGF-I replacement therapy, as noted in Figure 3, might be explained by periods of improved nutrition alone.

**Craniofacial Characteristics**

Affected children 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 (Fig. 4). 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 (Fig. 5) including those with normal appearing facies (Fig. 6)(56). 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 GHRD, as well as in GHD (57,58).

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 (59).

**Musculoskeletal and Body Composition**

Hypomuscularity is apparent in radiographs of affected infants, and is thought to be responsible for delayed walking despite normal intelligence and timing of speech onset (59). 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 GHRD demonstrated normal bone volume and formation rate, with reduction in trabecular connectivity. This study suggested that some of densitometry findings were artifactual, based on small bone size (60).

Limited elbow extensibility seen in most patients over 5 yr of age in the Ecuadorian population is an acquired characteristic, absent in younger children and increasing in severity with age (57,59). This feature is not peculiar to the Ecuadorian population or to IGF-I deficiency due to GHRD, recently confirmed by a Brazilian patient with GHRD with limited elbow extension (61) and observing this finding in all but the youngest patient in a family with eight individuals affected by multiple pituitary deficiencies (58). 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 (59).
Fig. 4. Front and profile views of 4-mo-old girl, homozygous for the E180 splice mutation of the GHR, demonstrating paucity of hair, prominent forehead, hypoplastic nasal bridge, shallow orbits, and reduced vertical dimension of the face, and profile view of a three-year-old patient from the initial report of Laron syndrome (6), demonstrating persistence of these features, and striking similarity with different genetic mutations. Reprinted from Trends Endocrinol Metab, vol 9, Rosenbloom, AL, Guevara-Aguirre J. Lessons from the genetics of Laron syndrome, pp 276–283, 1998, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.

Fig. 5. Comparisons of facial appearance between 52-yr-old patient (right upper panel) and her 76-yr-old mother (left upper panel) and 9-yr-old patient (right lower panel) and his 11-yr-old unaffected brother (left lower panel). Photos were taken at exactly the same distances. Note strong familial similarity but marked difference in facial dimensions. Reproduced from (59) with permission from Karger AG, Basel, Switzerland.
Fig. 6. Two women and two men from Ecuador with growth hormone receptor deficiency resulting from the E180 splice mutation of the GH receptor, demonstrating variation in craniofacial effects. From left to right, a 17-yr-old woman with height standard deviation score (SDS) –7.8, two years after menarche and a year after she stopped growing, a 19-yr-old woman 4 yr post-menarcheal with height SDS –6.5 (tallest female in the cohort), a 21-yr-old man with height SDS –7.6, and a 28-yr-old man with height SDS –9.2. Reprinted from Hormone and Metabolic Research, Volume 31. Rosenbloom AL. IGF-I deficiency due to GH receptor deficiency. Pages 161–171. Copyright 1999, with permission from Georg Thieme Verlag Stuttgart-New York.

Reproduction

Severe GHD is associated with small penis size with normal penile growth at adolescence or with testosterone treatment in childhood. This is also true of GHRD. Although puberty may be delayed 3–7 yr in some 50% of individuals, there is normal adult sexual function with documented reproduction by males and females (49). Females require C-section delivery.

Intellectual and Social Development

Intellectual impairment was originally considered a feature of the Laron syndrome (62). Among 18 affected children and adolescents administered 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 could not be addressed. In a followup study 25 years later, the investigators re-examined 8 of the original 18 patients and 4 new patients with GHRD, excluding 5 patients with mental disabilities who were in the original study (63). This group had mean verbal and performance IQs of 86 and 92 on the Wechsler scale without evidence of visual motor integration difficulties noted in the earlier group, but 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.

The recent description of intellectual impairment with severe IGF-I deficiency due to partial deletion of the IGF-I gene added concern about potential effects of severe IGF-I deficiency in utero (2). Nonetheless, patients with GH gene deletion and severe IGF-I deficiency have not been intellectually impaired (4), nor have those with severe IGF-I deficiency due to molecular defects in the GHRH-R (64). Sporadic anecdotal reports of patients with GHRD 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 (65). 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 (66).

The first controlled documentation of intellectual function in a population with GHRD 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 non-verbal 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, resulting in greater devotion to studies and superior achievement in school for IQ level (67).

The clinical findings of intellectual impairment with IGF-I gene deletion (2) and intellectual normality with GHRD is consistent with gene disruption studies in mice. The IGF-I deleted mouse is neurologically impaired, while the GHRD mouse is behaviorally normal (68,69). Thus, GHD dependent IGF-I production is not necessary for normal brain development and function.

**BIOCHEMICAL FEATURES**

**Growth Hormone**

Affected children 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 (7,48). The GH levels show normal diurnal fluctuation. Twenty-four-h profiles demonstrate marked GH variability among adult patients with suppression by exogenous recombinant human IGF-I (14). 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 may have normal or elevated basal levels of GH but invariably demonstrate hyper-responsiveness 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 vs 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 (7,49).
Absence of GHBP in the circulation was initially considered a requirement for the diagnosis of GHRD, 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 (7).

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 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 1 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 (59). 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 extremely low or undetectable levels of GHBP serves as an important diagnostic feature, it is not a sine qua non for the diagnosis of GHRD.

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 GHRD. 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 (7).

Among 50 Ecuadorian patients homozygous for the E180 splice-site mutation, IGF-I levels were significantly greater in adults 16–67 yr of age (n = 31, 25 ± 19 µg/L) than in the 19 subjects under 16 y of age (3 ± 2 µg/L, p < 0.0001), although still markedly below the normal range of 96–270 µg/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 µg/L vs 70 ± 42 µg/L, normal 388 to 792 µg/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 -II with adulthood suggest effects on synthesis of these growth factors which are not mediated through the GHR and are presumably 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 severe short stature from GH deficiency resulting from GHRH receptor mutation and affected children have comparably very low IGF-I (and IGFBP-3) serum concentrations (64). The correlation of IGF-I levels with stature in adults with GHRD 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 GHD or GHRD, IGFBP-3 is reduced, and in children and adults with GHRD this reduction correlates with statural impairment (1). In renal disease, elevated IGFBP-3, as well as IGFBP-1 and IGFBP-2, are thought to impair the delivery of normal levels of IGF-I (5).

Short term and extended treatment of GHI with IGF-I has failed to result in increases in IGFBP-3 (14,70–74), 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-I is elevated in GHD and GHRD; in GHRD 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 GHRD and 175% of control in affected adults, a significant difference. The IGFBP-3 levels in adults with GHRD are significantly greater than those in affected children (75).

Diagnostic Issues in GH Resistance

GHI/GHRD is readily diagnosed in its typical and complete form because of: severe growth failure; the somatic phenotype of severe GHD; 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 1, some of the biochemical features of GHRD may be shared by conditions associated with acquired GH insensitivity, such as malnutrition and liver disease. In a large multinational study designed to identify patients for replacement therapy with recombinant human IGF-I (rhIGF-I), a scoring system was developed which assigned one point for each of the following:

- Height > 3 SD below mean height for age
- Basal GH > 2.5 µg/L
- Basal IGF-I <50 µg/L
- Basal IGFBP-3 < –2 SD
- IGF-I rise with GH (0.05 mg/kg/d × 4 d) < 15 µg/L
- IGFBP-3 rise with GH stimulation < 0.4 mg/L
- GH binding < 10% (based on binding of 125I-hGH)

A score of 5 out of the possible 7 was considered diagnostic for GHR deficiency. This standard resulted in identification of 82 patients from 22 countries who reflect a wide variability for each criterion. Particularly noteworthy was that height SDS range was up to –2.2 (76). These criteria recognize the age and sex (after age 7 yr) variation of IGFBP 3 by using a standard of < –2 SD but, oddly, designate a fixed standard for IGF-I which is within the range of normal for children under age 7 (Table 3).

As noted above, the presence 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. (65) 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 GHRD. Identification of heterozygous mutations, however,
is not necessarily helpful because, as noted earlier, polymorphisms have been described that appear to have no phenotypic consequences.

**Partial GH Resistance**

It is reasonable to consider that, as with GH deficiency, GH resistance might be expected to occur in an incomplete form, as is also seen with insulin resistance, androgen insensitivity, and thyroid hormone resistance. Affected children might have growth failure with normal or slightly increased GH secretion, low normal or slightly decreased GHBP levels, decreased IGF-I concentrations, but not as severely reduced as in complete GHD or GHRD, and they 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. As noted above, two such defects have been described. GHBP concentrations are low in children with idiopathic short stature (ISS, i.e., short children without a recognizable syndrome or GHD). Using a ligand mediated immunofunction assay Goddard et al. (35) studied a large number of short children with known causes of growth failure such as GHD 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 concen-
trations below the control mean and nearly 20% had concentrations that were two standard deviations or more below the normal mean for age and sex. To explore the possibility that these low GHBP concentrations might indicate partial GHI, molecular genetic analysis was done in 14 children with ISS who had low GHBP concentrations and normal GH secretion. Five GH receptor mutations were detected in four children. In one patient, there was compound heterozygosity involving mutations in exons 4 and 6. The other 3 patients were heterozygous for mutations in the GHR with no defects in the other allele. The method used could have missed additional mutations and there might also be involvement of the regulatory domains of the GHR. None of these patients had the clinical phenotype of GHD. Three of the four patients were treated with GH and had modest improvement in growth velocity in the first year. This modest response could be due to GH resistance or simply to the fact that they were not IGF-I deficient.

Whether the distribution of GHBP concentrations in ISS indicates that partial GHI is an important cause of short stature remains to be demonstrated. The 14 subjects studied by Goddard et al. (35) were selected from the large US National Cooperative Growth Study database. Thus, if other heterozygous mutations of the GHR besides those described as having a dominant negative effect ultimately prove to be one cause of partial GHI, this would explain only a very small proportion of ISS.

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 (77). Subcutaneous preparations of rhIGF-I became available in 1990.

**Short Term Effects of IGF-I Treatment in GHRD**

**INTRAVENOUS (IV) ADMINISTRATION**

The hypoglycemic effect of an iv bolus of IGF-I (75 µg/kg) following an overnight fast was demonstrated in 9 patients with GHRD aged 11–33 yr. The hypoglycemia was symptomatic and associated with a fall in plasma insulin level with recovery only after food was taken at 2 h post-injection. Marked increase in serum GH concentration in the seven older individuals reflected the overriding effect of hypoglycemia stimulation, despite the expected SS response to the increased levels of free IGF-I (78). Suppression of TSH levels provided indirect evidence of SS stimulation (79). The elimination time for iv injected IGF-I was found to be markedly reduced in 3 children and 7 adults with GHRD compared to 3 healthy children and 3 healthy adults, presumably due to the absence of IGFBP-3 in the patients (80). IGF-I given iv to a 9-yr-old child for 11 d demonstrated substantial anabolic effects, including decreased serum urea nitrogen, increased urinary calcium excretion, and decreased urinary phosphate and sodium excretion. As previously noted with iv IGF-I in normals, IGF-II levels were suppressed and asymptomatic hypoglycemia noted (81).

**SUBCUTANEOUS (SC) ADMINISTRATION**

There was no significant hypoglycemia with IGF-I in a dose of 120–150 µg/kg/d sc for 7 d, followed by breakfast. Plasma GH was markedly reduced, and type 3 procollagen (a growth marker) increased (82). Hypoglycemia did not occur with IGF-I sc at a dose of 40
µg/kg every 12 h over 7 d in 6 Ecuadorian adults with GHRD, although insulin levels were suppressed. There was a two-fold increase in urinary calcium excretion without a change in serum calcium levels. Mean integrated 24 h GH levels were suppressed, as were the number of peaks, the area under the curve, and clonidine stimulated GH release. The mean peak serum IGF-I levels were 253 ± 11 ng/mL reached between 2–6 h after injection and mean trough levels were 137 ± 8 ng/mL before the next injection, values not significantly different from those of normal control Ecuadorian adults. As previously noted, IGF-II levels decreased and correlated inversely with IGF-I levels, indicating that IGF-I was displacing IGF-II from available IGFBPs. There were no significant changes in the half-life or metabolic clearance of IGF-I between d 1 and 7, although the distribution volume did increase over this time. Although IGFBP-3 levels did not increase, elevated baseline IGFBP-2 levels (153% of control) increased 45% (p < 0.01) (14).

The short-term studies demonstrated that there was an insignificant risk of hypoglycemia in the fed state with sc administration of IGF-I, 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 (80), with blunting of the therapeutic effect. Four children and 4 adults with GHRD treated for 7 d with a single daily subcutaneous injection of IGF-I in a dose of 120–150 µg/d experienced a significant decrease in serum IGFBP-3 levels measured by specific RIA (83). As noted above, Vaccarello et al. (14) did not find a significant change in IGFBP-3 levels following 7 d of twice daily sc injection of doses of IGF-I sufficient to raise serum levels to normal in adults with GHRD. Further studies found that the two forms of IGFBP-3 associated with IGF and ALS, which are able to form the ternary 150-kDa complex were abnormally distributed in these GHRD patients. This distribution was unchanged by IGF-I treatment that, in addition to not increasing the IGFBP-3, did not increase ALS levels (70). Although it was hoped that chronic treatment would result in stimulation of ALS and IGFBP-3, this did not seem likely in view of the experience with GH treatment of GHD. In this situation, where serum IGFBP-3 levels are also reduced, exogenous GH rapidly increases IGFBP-3 levels (84).

**Long-Term Treatment with IGF-I in GHI**

In addition to concerns regarding the failure of short-term therapy to increase IGFBP-3 levels, there was concern whether catch-up growth in children with GHI due to GHRD or to GH antibodies would be as substantial as occurs with GH replacement therapy in patients with GHD in the absence of a direct effect of GH on bone (15). Growth acceleration comparable to that seen with GH treatment of GHD was reported in 5 children aged 3.3–14.5 yr with GHRD treated for 3–10 mo with single daily doses of 150 µg/kg. Baseline growth velocities of 2.8–5.8 cm/yr increased by approx 1.5–4 fold to 8.8–13.6 cm/yr, with the youngest patients responding most impressively. A reduction of subcutaneous fat, measured by skin-fold thickness, was noted in the four patients who were considered obese. In contrast to the single daily dosage of 150 µg/kg administered by Laron et al. (85), Walker et al. (86) gave 120 µg/kg twice daily to a 9.7-yr-old child with GHRD with a change in growth velocity from 6.5 to 11.4 cm/yr over a 9 mo period. Although mean pre-treatment IGF-I levels of 9 ± 2 µg/L increased to 347 ± 26 µg/L after 2 h, serum concentrations of IGF-II were unchanged, contrasting with earlier short term studies. Serum and urinary urea nitrogen decreased while creatinine clearance, urine volume, and urinary calcium increased. There were no abnormalities in glucose metabolism.
The first report of treatment for longer than 10 mo was in two children with GHRD with pre-treatment growth velocities (GV) of 4.3 and 3.8 cm/yr at 8.4 and 6.8-yr of age, respectively. They had suppression of greatly elevated serum GH levels and increase in procollagen I levels shortly after starting treatment; 6 mo GV increased to 7.8 and 8.4 cm/yr, without side effects. In the second 6 mo of treatment GV decreased to 6.6 and 6.3 cm/yr and in the subsequent 5 mo growth rate returned to pre-treatment values. Improvement in bone density was documented by dual photon absorptiometry. These patients were treated with a dose of 40 µg/kg sc twice daily and the waning of their growth response after a year indicated that this dosage was not adequate for sustained effect (87).

Since 1995, data have become available on 70 patients with GHI treated with subcutaneous injections of IGF-I for 12 mo or longer. Seven of these patients were resistant to GH because of GH inhibiting antibodies developing after treatment with GH injections for GHD due to GH gene deletion. The rest of the patients had abnormalities in GH receptor function, including Pakistani and Arab patients thought to have post-receptor defects (46–48). The largest group of patients was recruited for the international multicenter study which included 33 patients from 12 countries, 3.7–23 yr-of-age, 2 with GH gene deletion and the rest with GHRD. 1-yr growth data were reported for 26 of these patients and 2-yr data for 18. The 7 patients not reported include 2 who stopped treatment before 12 mo because of insufficient growth response and 5 because of adverse events. 3 did not continue for a full 24 mo because of poor compliance, headache, and weight gain. In the entire group treated for 1 yr, average height SDS gain was 0.7; for the subgroup treated for more than 12 mo, first-year average gain was 0.8 SDS and over 2 yr, 1.2 SDS. Serum IGF-II levels decreased and IGFBP-3 concentrations remained constant during this long term therapy (74). The most recent report of the European study provided data on 17 patients treated for 48 mo or more. The overall increase in height SDS was 1.67 ± 1.16 (from −6.52 ± 1.34 to −4.85 ± 1.81) with an increase in BMI-SDS from 0.59 ± 1.82 to 1.83 ± 1.50. Interestingly, gain in BMI correlated with improvement in SDS for height in this group. The gain in BMI was postulated to be the result of insulin like effects during the peak times following IGF-I injection; fat cells lack IGF-I receptors, but high doses of IGF-I can have an insulin like effect by binding to the insulin receptor (88). The adverse events noted were headache, hypoglycemia, papilledema (1 instance), Bell’s palsy (1 instance), lipohypertrophy, and tonsillectomy/adenoidectomy (3 instances).

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 µg/kg bid) and LRH analog to forestall puberty. A girl age 18 and boy age 17.5 yr, with bone ages of 13.5 and 13 yr experienced an approximate tripling of growth velocity, increased bone mineral density, and maturation of facial features on IGF-I for one year. There was initial loss of fine straight hair followed by recovery of denser and curly hair with filling of the fronto-temporal baldness, the appearance of axillary sweating, loss of deciduous teeth, and appearance of permanent dentition. The boy had coarsening of his facial features (Fig. 7). Submaxillary gland enlargement was also noticed in one patient and fading of premature facial wrinkles, commonly associated with GHD, noted in the other patient. Serum IGF-I levels were seen to increase into the normal range during the first 2–8 h following IGF-I injection (89). Studies were done at doses of 40, 80, and 120 µg/kg with pharmacokinetic profiles suggesting a plateau effect between 80 and 120 µg/kg per dose. It was considered that the carrying capacity of the IGFBPs was saturated at this level (71). As previously noted, 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 (71).

Tachycardia was noted in these adolescent patients and further studied in 16 prepubertal Ecuadorian patients during induction of treatment at progressive dosages of 40, 80, and 120 µg/kg bid. Both repeated palpation of the radial artery and continuous portable Holter monitoring were used. There was a direct dose related increase to approx 25% of baseline rate at the highest dosage. This was unrelated to glucose or electrolyte changes which were not significant (90).

Seventeen prepubertal Ecuadorian patients were entered into a randomized double blind, placebo controlled trial of IGF-I at 120 µg/kg sc bid for 6 mo, 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 9 placebo-treated patients had a modest but not significant increase in height velocity from 2.8 ± 0.3 to 4.4 ± 0.7 cm/yr, entirely attributable to 3 individuals with 6-mo velocities of 6.6–8 cm/yr. Although this response was thought to be the result of improved nutritional status, there was no accompanying increase in IGFBP-3 as noted with nutrition-induced catch up growth by Crosnier et al. (55) in their GHRD patient with anorexia. For those receiving IGF-I, the height velocity increased from 2.9 ± 0.6 to 8.8 ± 0.6 cm/yr and all 16 patients had accelerated velocities during the second 6 mo period when all were receiving IGF-I. No changes or differences in IGFBP-3 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. One patient had asymptomatic papilledema developing one month after

Fig. 7. Face and hair changes in 17.7-yr-old patient (bone age 13-yr) with GHRD during 6 mo treatment with IGF-I, 120 µg/kg bid and depot GnRH agonist begun at age 16.5-yr. Reproduced from Rosenbloom AL. IGF-I treatment of growth hormone insensitivity. In: Rosenfeld RG, Roberts CT (eds.) The IGF System: Molecular Biology, Physiology, and Clinical Applications. Copyright 1999, with permission from Humana Press, Totowa, NJ; pp. 739–769.
beginning IGF-I therapy that spontaneously resolved over several weeks without interrupting treatment. Six of the seven IGF-I treated patients experienced hair loss (72).

Two-yr treatment results in the Ecuadorian group have been reported, with comparison of the 120 mg/kg bid dosage to 80 mg/kg bid and also comparison of growth responses to those of GH treated GHD in the same population. There were no baseline differences between the low and high-dose groups for growth velocity, bone age, SDS for height, or mean % body weight for height (MBWH). No significant differences in GV or changes in height SDS, height age, or bone age between the 2 dosage groups were seen and a group of 6 subjects receiving the higher dose followed for a third year continued to maintain second year growth velocities. Improvement in mean height SDS over the 2-yr period was 1.5 for the higher dose and 1.3 for the lower dose, compared to 1.2 in the international study; in both the international and Ecuadorian cohorts, two-thirds of the 2-yr height SDS gain was in the first year. The annual changes in height age in both the first and the second year of treatment of the Ecuadorian children correlated with IGF-I trough levels which tended to be in the low normal range despite a failure of serum IGFBP-3 levels to increase (Fig. 8). The comparable growth responses to the two dosage levels and the similar IGF-I trough levels were thought to confirm the plateau effect at or below 80 \( \mu \text{g/kg body weight twice daily} \) (73).

Comparison of the growth responses of the 22 IGF-I treated GHRD patients to those of 11 GH treated GHD subjects in the same setting demonstrated GV increments in those with GHRD to be 63% of those achieved with GH treatment of GHD in the first year and less than 50% in the second and third years of IGF-I treatment. The GHRD group, however, did not differ from those with GHD in the change in bone age or in the ratio of height age to bone age changes over the 2-yr period. There was a greater change in % MBWH in the GHRD group treated with IGF-I, which, as noted by Ranke et al. (88), might reflect the insulin like action of the levels of IGF-I, contrasting with the lipolytic effect of GH replacement therapy. The difference in growth response between IGF-I treated GHRD and GH treated GHD was consistent with the hypothesis that 20% or more of GH influenced growth is due to the direct effects of GH on bone (15). Nonetheless, the comparable ratios of height age change to bone age change suggested similar long term effects for replacement therapy in these two conditions (73).

The Israeli report of 3 yr treatment of 9 patients, including the 3 with a presumed post-receptor defect, is the only one in which patients were given IGF-I as a single daily dosage (150–200 \( \mu \text{g/kg} \)). While the European and Ecuadorian study groups noted mean height SDS improvement of 0.7–1.0 over 1 yr and 1.2–1.5 over 2 yr, the Israeli patients had an improvement of only 0.4 over 1 yr and for the 6 with 2 yr data, 0.2 over 1 yr and 0.4 over 2 yr (91). The kinetic studies that originally formed the rationale for twice daily administration are supported by these observations. Of the 5 patients completing 3 yr of IGF-I treatment in the Israeli report, 3 were growing at slower rates than before treatment while the other 2 remained at comparable velocities to the second year of treatment. The subgroup with normal IGFBP-3 levels is particularly interesting, because the growth responses do not differ from those of the rest of the group, suggesting that the IGFBP-3 deficiency is not the explanation for the relatively deficient growth response to replacement therapy with IGF-I when compared to GH treatment of GHD (46). 2 prepubertal girls and 2 adult women with GHRD in Israel developed clinical features of hyperandrogenism and elevated androgen levels during treatment with IGF-I (92).

Five children with GHRD and 3 with growth attenuating antibodies to GH have been treated for 4 yr by Backeljauw and colleagues (93). The 2 yr data are comparable to data
in the European and Ecuadorian populations, with an improvement in height SDS over the 2 yr period of 1.1. Bone age was noted to advance consistent with chronologic age. There was rapid growth of the spleen and kidney, as determined by ultrasound during the first year with a slowing of spleen growth but a continued rapid kidney growth during the second year. In a preliminary report, the third year and fourth year results of treatment in this group were reported; a further decrease in height velocity to a mean 5.1 cm/yr occurred during the third year, but the fourth year mean height velocity was 5.7 cm/yr. Kidney growth continued in 5 of the 8 patients who had renal length for height at or above the 95th percentile. There were no functional or structural abnormalities of the kidneys, however (94). In 5 of these patients, craniofacial growth has been monitored with the suggestion of mandibular overgrowth, most noticeable in the last 2 yr of treatment (95).

A Vietnamese girl treated by Walker et al. (96) with IGF-I and LHRH analog had modest improvement of growth over the first 3 yr of treatment, a height SDS increase of 1.2 with dramatic slowing of growth response thereafter. As with the patient in Fig. 7, facial coarsening was noted.

**CONCLUSION**

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 acromegoid facial changes, why then do we not see sustained growth acceleration as in GH treated GHD? The administration of IGF-I with recombinant IGFBP-3 would be an important clinical study to determine how
much of this deficit is due to IGFBP 3 deficiency. The dual effector hypothesis remains the best explanation for inadequate growth response (15). 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. The comparable ratios of change in height age to change in bone age over 2 yr of treatment in GHI children treated with IGF-I and GHD children treated with GH, however, suggest that the absence of a direct GH effect in GHI may have a temporal, rather than absolute effect on long-term response to treatment (73). Thus, IGF-I replacement therapy of GI may need to continue longer than GH treatment of GHD to achieve normal height. This goal will likely require suppressing adolescence in most children with GHI, using GnRH analogs (89).

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. Normalization of craniofacial features has also been apparent (97). Voice change has not been remarked on, but can be expected. It is likely that maintenance of body composition changes will require continued treatment in adulthood.

The reduction of risk factors for the higher mortality in infancy and childhood with GHRD is to be expected with IGF-I therapy, but the reason for this increased risk is unknown. Leukocytes share in the general up regulation of IGF-I receptors in GHRD, and appear to function normally in this condition (98). In a study of one affected infant (who died at 7 mo with bronchitis) and 5 adults with GHRD from Ecuador, Diamond et al. (99) demonstrated a variety of immune disturbances in the infant and 3 of the adults. The pathologic significance of these findings remains uncertain (100).

The ability to resolve the many remaining questions about treatment to attain normal stature and body composition in GHI is thwarted by the decision of the few manufacturers to no longer synthesize IGF-I. This decision was based on the inability to identify a substantial market to justify the costs of manufacture and regulatory clearance.

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