J Endocrinol Invest (2016) 39:19–28
DOI 10.1007/s40618-015-0327-2

REVIEW

Growth hormone insensitivity: diagnostic and therapeutic approaches

S. Kurtoğlu[1] · N. Hatipoglu[1]

Received: 4 October 2014 / Accepted: 21 May 2015 / Published online: 11 June 2015
© Italian Society of Endocrinology (SIE) 2015

Abstract
Introduction Growth hormone resistance defines several genetic (primary) and acquired (secondary) pathologies that result in completely or partially interrupted activity of growth hormone. An archetypal disease of this group is the Laron-type dwarfism caused by mutations in growth hormone receptors. The diagnosis is based on high basal levels of growth hormone, low insulin like growth factor-I (IGF-1) level, unresponsiveness to IGF generation test and genetic testing. Recombinant IGF-1 preparations are used in the treatment
Conclusion In this article, clinical characteristics, diagnosis and therapeutic approaches of the genetic and other diseases leading to growth hormone insensitivity are reviewed.

Keywords Growth hormone · Insensitivity · IGF-1 generation test · Recombinant IGF-1

Introduction

Hypothalamic growth hormone releasing hormone (GHRH) stimulates the secretion of growth hormone (GH) by the somatotropic cells of the anterior pituitary gland, whereas hypothalamic somatostatin inhibits its secretion. The secretion is regulated by the balance between neurological, metabolic and endocrine factors. While half of GH is carried by a binding protein (GHBP) which is considered to be a part of the receptor, remaining is found in unbound form. GH binds to its receptor and results in receptor dimerization, thus initiates intracellular effects. At the end of these effects it induces synthesis of the insulin-like growth hormones (IGFs; IGF-1 or 2) in the liver. IGF-2 is major fetal growth factor, synthesized in uteri or in tumor status in contrast to IGF-1, which is a major growth factor, produced throughout life. IGFs are bound to one of the six binding proteins called insulin like growth factor binding proteins (IGFBPs). Insulin like growth factor binding protein-3 (IGFBP-3) is the most abundant of them, and accounts for 75–90 % of circulating IGF-1 and nearly 1 % of the circulating IGF-1 is unbound. Insulin like growth factors (IGF-1 or 2), come together with one of the carrier proteins (IGFBP) and forms a complex; called as "binary complex''. Binary complexes are formed in a low rate. If the acid-labile subunit (ALS), which is synthesized in the liver, is involved, the complex is then named as "ternary complex". In other words, the complexes involving IGF1 or 2 and IGFBP-3 or 5 along with ALS, are ternary complexes. The ternary complexes restrict the levels of circulating IGF-1 and 2, prolong their half- lives and prevent hypoglycemia. Increasing serum IGF-1 levels inhibit GH secretion due to a feedback mechanism [1–4].

Insensitivity to growth hormone comprises a large spectrum of clinical manifestations related to the absence of the biological effects of GH. Though having similar phenotype with GH deficiency, high levels of circulating GH are found. Low IGF-1 levels prevent GH suppression in these cases. The "Laron-type dwarfism" is the most severe clinical manifestation of the insensitivity to growth hormone. Laron first described this syndrome in 1966 in three siblings, presenting with severely retarded development and high serum GH levels and then 22 cases were recruited within 2 years [5, 6]. Later on, case series and mutation studies have been published in Ecuador and Turkey [7, 8].

✉ N. Hatipoglu
nihalhatipoglu@yahoo.com

[1] Department of Pediatric Endocrinology, Medical Faculty, Erciyes University, 38039 Kayseri, Turkey

Table 1 Classification of growth hormone resistance

I. Primary growth hormone resistance (insensitivity) = Laron syndrome (hereditary/congenital defects)
Growth hormone receptor defects (qualitative, quantitative, extracellular, transmembrane or intracellular mutations)
Growth hormone signal transduction abnormalities (post-receptor defects, STAT5b)
Primary defects of IGF-1 synthesis (IGF-1 gene mutations), IGF-1 receptor deficiency, bio-inactive IGF-1, IGFBP-3/acid labile subunit (ALS) mutations
Other conditions: bioinactive growth hormone (Kwarsky syndrome)
II. Secondary growth hormone resistance (insensitivity) disorders (acquired conditions, occasionally transient), possibly partial
Antibodies against growth hormone: in cases of GH gene deletions (isolated GH deficiency type IA) the administration of growth hormone results in the formation of antibodies
Antibodies against the growth hormone receptor
Insensitivity to growth hormone in cases of malnutrition, inflammatory bowel diseases, severe diseases and catabolic state
Insensitivity to growth hormone in liver diseases (Alagille syndrome and others)
Insensitivity to growth hormone in poorly controlled diabetes
Other conditions: Idiopathic short stature, Turner syndrome, Noonan syndrome (PTPN11 mutations)

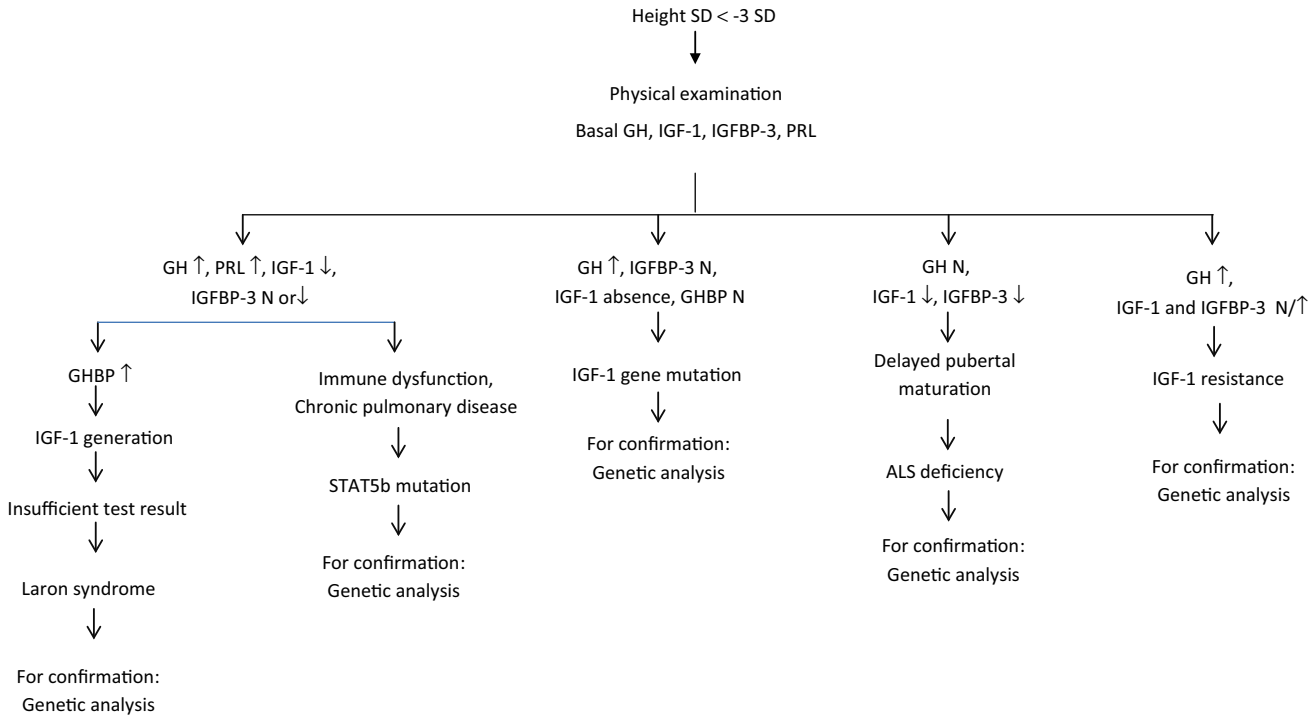


Fig. 1 Algorithm for management of growth hormone insensitivity. *SD* standard deviation, *GH* growth hormone, *IGF-1* insulin like growth factor-1, *PRL* prolactin, *IGFBP-3* insulin like growth factor binding protein-3, *GHBP* growth hormone binding protein, *STAT5b* signal transducer and activator of transcription 5b, *ALS* acid labile subunit and *N* normal

The diagnosis of growth hormone resistance: is made by high initial levels of GH along with low IGF-1 levels and lack of any increase at the IGF-1 and IGFBP-3 levels following exogenous growth hormone administration.

Definitions

After publishing the first cases, investigators reached a consensus on the terminology and classification of the

Table 2 Clinical and laboratory findings in Laron-type dwarfism

I. Growth
Normal birth weight, normal or short birth length
Severely retarded growth beginning at birth (−3 to −10 SD), growth velocity is around the half of the normal
The deviations in height are low and correlate with low IGF-1 and IGFBP-3 levels
Although the bone age is retarded, it is advanced compared to the height
Small hands (under the tenth percentile for height) and small feet (70 %)
Normal body segments based on bone age, abnormal upper- to-lower body segment ratio and arm span in adults
Craniofacial features
Sparse hair before the age of seven (70 %) and frontal and temporal recessions at all ages
Prominent forehead
Although the head circumference is normal for age, it may be defined as large for the age
Hypoplastic nasal root and shallow orbit
Reduced vertical diameter of the face
Sunset appearance of the eyes (25 %), blue sclera, unilateral ptosis, depressed under eye with dark circles under the age of ten
Delayed onset of teething, prolonged retention of the primary teeth, dental caries, normal occlusion of the permanent teeth, lacking third molar
Sculpture-like mandibular structure
Facial asymmetry (15 %)
II. Musculoskeletal, body composition
Underdeveloped muscles, delay in walking
Hip dysplasia, avascular necrosis of the femoral head (25 %)
A high-pitched voice in children and in most of adults
Thin skin and premature skin aging
Reduced range of motion of the elbow (acquired 85 %, after the age of 5)
Low body weight in proportion to the height, most of adults are obese in proportion to the height
Osteopenia
III. Metabolic problems
Fasting hypoglycemia (more prominent in the newborn and infant)
Intolerance to fasting
High total cholesterol and LDL-cholesterol levels
Decreased sweating
IV. Sexual development
Small penis size in children, normal sexual development in adolescents
Delayed puberty (50 %)
Normal reproductive functions

insensitivity (resistance) to growth hormone in 1993 (Table 1; Fig. 1) [3, 6, 9–11].

Primary growth hormone resistance (insensitivity)

Growth hormone receptor defects

This condition, which is known as Laron-type dwarfism, is a functional GH receptor deficiency. The GH receptor gene is located on the short arm of the chromosome 5 [3]. A variety of heterozygous mutations has been found in the patients. Children with Laron syndrome present with extreme short stature, insufficient linear growth, and retarded skeletal maturation. Their craniofacial characteristics reflect the underdeveloped facial bones. Craniofacial changes may be mild or quite prominent, based on the intensity of the resistance. Another major symptom of Laron syndrome is progressive obesity starting in early childhood. This obesity is characterized by high body fat, especially an increase in the arms adiposity [12]. Clinical and laboratory characteristics of the patients are given in Table 2 [1, 3, 6, 7, 13–15] and Table 3 [4, 16].

The diagnosis is based on standard auxology data and typical somatic features, basal laboratory tests, left wrist radiography, pharmacological GH stimulation test, IGF-1 generation test and genetic studies. In GH stimulation test, high basal GH levels (>2.5 ng/ml) along with normal GH

Table 3 Clinical and laboratory characteristics of the cases with defects in the growth hormone-IGF-I axis

Problem	Affected Gene	Prenatal Growth	Postnatal Growth	GH-IGF-1 axis	Other findings
Laron syndrome	GHR	Birth weight N Length N or short	↓↓↓	GH↑, PRL↑, IGF-1↓, IGFBP-3 N-↓, GHBP ↑	Frequent hypoglycemia Generally homozygous
STAT5b deficiency	STAT5b	Normal	↓↓↓	GH↑, IGF-1 ↓, IGFBP-3 N-↓, PRL ↑	Immune deficiency Generally homozygous
IGF-1 gene mutation	IGF-1	↓↓↓	↓↓↓↓	GH↑, IGF-1 absent, IGFBP-3 N, GHBP N	Deafness Microcephaly Carbohydrate intolerance Homozygous
Russel-Silver syndrome	IGF-2 abnormal cytosine Cytosine methylation	↓↓↓	↓↓↓↓	GHN, IGF-1 N, IGFBP-3 N, IGF-II N	Asymmetric face Dysmorphic characteristics
ALS deficiency	IGFALS	Normal	↓–↓↓	GH N, IGF-1↓, IGFBP-3↓, ALS undetectable	Homozygous Phenotype is similar to delayed growth and adolescence
IGF-1 resistance	IGFR	↓↓–↓↓↓	↓↓↓	GH N-↑, IGF-1 N-↑, IGFBP-3 N-↑	Hemizygous Heterozygous or compound heterozygous Mental retardation
Alagille syndrome	JAGI	↓↓	Mild to moderate	GH↑, IGF-1↓, IGFBP-3 N, GHBP ↑	Autosomal dominant Typical facial appearance
Chronic kidney disease	–	Normal	Moderate to severe	GH N, IGF-1↓, IGFBP-3 ↑, GHBP ↓	General findings
GH inhibitor antibodies, isolated GH deficiency Type 1 A, GH-1 gene mutation	–	Normal	Severe	GH deficient, IGF-1↓↓↓, IGFBP-3 ↓↓, GHBP N	Growth retardation

Modified from the references [3, 15]

GH Growth hormone, *GHwR* growth hormone receptor, *GHBP* growth hormone binding protein, *IGF-1* insulin like growth factor 1, *IGFBP-3* insulin like growth factor binding protein 3, *PRL* prolactin and *ALS* acid labile subunit

response (>10 ng/ml), following stimulation but significantly low IGF-1 levels and low ALS, IGFBP-3 and GHBP levels are highly suggestive of a diagnosis of Laron syndrome. However, the GHBP levels may be found as normal or even high in 25 % of the cases of Laron syndrome [17]. Furthermore, generation test using GH, results in insufficient increases in the levels of IGF-1 and IGFBP-3 (Table 5) [17]. Induced prolactin levels are high in these cases. Serum thyroid and adrenal hormone levels are within normal limits. Although gonadotropins and sex hormones appear to be low, they are within normal range in reference according to bone age. Differential diagnoses are made based on the other clinical and laboratory characteristics of the diseases. The IGFBP-1 and 2 levels are high in these patients, whereas the serum IGF-II levels are normal. In spite of low blood glucose, insulin and free fatty acid levels are high in the patients. Insulin resistance increases with age and obesity and may progress to glucose intolerance and type 2 diabetes. Data demonstrate that leptin is increased in patients with homozygous GHI, probably reflecting abnormalities of body composition and metabolism typical of this condition [18]. Serum alkaline phosphatase, inorganic phosphorus and creatinine levels are high. Normal initial total and LDL-cholesterol levels increase with age and obesity [10].

IGF-1 generation test

While adequate increases are observed in the levels of IGF-1 and IGFBP-3 in the cases of GH deficiency, neurosecretory dysfunction and bio-inactive GH (Kowarski syndrome), insufficient increases are seen in Laron-type dwarfism and idiopathic short stature. If basal GH level is high and IGF-1 level is significantly low or normal or exaggerated GH levels are detected in two GH stimulation tests, a IGF-1 generation test is performed. Low serum IGF-1 levels may be detected in GH deficiency, GH resistance, signaling defect (STAT5b), IGF-1 gene defects, ALS deficiency, liver diseases, malnutrition, hypothyroidism, delayed puberty, poorly controlled diabetes, chronic diseases and glucocorticoid therapy [16]. IGF-1, IGFBP-3 and ALS increases may be determined by the IGF-1 generation test. The IGF-1 generation test should be scheduled for at least 30 days later in patients who underwent a GH stimulation test [19]. Various protocols have been determined for this test. First, Rudman performed IGF-1 measurements after administering GH during 10 days [20]. Spiliotis et al., Darendeliler et al., Cotterill et al., administer GH subcutaneously at a dose of 0.1 units daily for four days and draw blood samples in the morning of the fourth day at 09:00 A.M. (8–16 h after the last injection) to measure IGF-1 and BP-3 levels [19, 22]. Fasting IGF-1 and BP-3 levels are routinely determined on the first day and GH was administered every evening. On the other hand, Spiliotis et al., collect fasting blood sample at the baseline and initiate GH injections and perform the measurements on the days 1, 2, 3, 4 and 5. A threefold increase at the level of IGF-1 or reaching the upper limits of normal is expected during the 4-day test [19]. Darendeliler et al. determined insufficient annual growth velocities in patients who revealed an increase of approximately 400 ng/ml at the level of IGFBP-3 in this test and emphasized that this binding might be an important criterion for GH deficiency. Moreover, in the generation test performed, children with idiopathic short stature, delta IGF-1 was found as 31 % and delta BP-3 was found as 7 % [21]. Chrysis et al. detected an increase of 104 ± 37 % at the IGF-I level and an increase of 38 ± 14 % at the IGFBP-3 level in the prepubertal control group, whereas these rates were found as 101 ± 23 and 52 ± 36 %, respectively, in the beta-thalassemia patients with normal stature [23]. Spiliotis et al. performed generation tests in the GH deficiency, neurosecretory dysfunction and control groups and interpreted the results (Table 4). The peak level was obtained on the day 4 or 5 in the control group while it occurs on day 3 or 4 in GH deficiency [19]. In addition, one demonstrated that the prepubertal responses and pubertal responses were different. The effects of sex hormones on IGF-1 production and GH sensitivity during pubertal stage have not been clearly determined [24].

Table 4 Prepubertal and pubertal results of IGF-I generation test in normal children and children with GH deficiency or neurosecretory dysfunction

Groups	IGF-1 increases (%)	
	Prepubertal	Pubertal
GH deficiency	516 % ± 58	191 % ± 28
Neurosecretory dysfunction	433 % ± 50	141 % ± 20
Normal stature controls	106 % ± 12	48 % ± 8
Short stature controls	102 % ± 18	61 % ± 17

Considering that the short generation test results may not be clear in some cases and certain groups may overlap with one another, Buckway et al. developed 7-day low-dose and high-dose tests [24, 25]. A daily dose of 0.025 mg/kg of GH is administered during the low dose test, while a daily dose of 0.05 mg/kg is administered during the high-dose test and blood samples are collected on the day 8. When an increase under 15 ng/ml in the IGF-1 level is considered as a criterion for GH insensitivity, overlapping is observed in the low-dose test, however, the specificity of the IGFBP-3 value achieves 92 % and its sensitivity achieves 100 % in diagnosing GH insensitivity [24, 26].

In the bio-inactive growth hormone (Kowarski syndrome) syndrome, the generation test results in an increase of 30 ng/ml at the level of IGF-I and an increase of 400 ng/

Table 5 Scoring system for growth hormone resistance

Test	Parameter	Criterion	Score*
Auxology	Height	−3 SD	1
Basal GH	GH	>2.5 ng/ml	1
Basal IGF-1	IGF-1	≤50 ng/ml	1
Basal IGFBP-3	IGFBP-3	−2 SD	1
IGF-1 generation (4 day 0.1 U/kg GH)	Increase in n IGF-1 level Increase in IGFBP-3 level	≤15 ng/ml ≤400 ng/ml	1
GH binding	GH binding %	10 %	1

* 5 and higher scores support the diagnosis of growth hormone resistance

ml at the level of IGFBF-3. The increases in the Laron-type dwarfism are under 15 and 400 ng/ml for IGF-1 and IGFBF-3, respectively.

Although various protocols exist, any consensus has not been reached on the method and interpretation of the IGF-1 generation test. As a matter of fact, a survey conducted among the members of the European Society for Pediatric Endocrinology (ESPE) revealed that more than ten protocols have been used to perform IGF-1 generation during the last 2 years and the positive predictive value of the test was low. Therefore, the limited contribution of the IGF-1 generation test for diagnosis and treatment decision was emphasized [27].

Growth hormone resistance is scored by auxology and laboratory tests (Table 5) [17]. A total score of ≥5 supports the diagnosis of Laron-type dwarfism. Although scoring may be considered as a rough method, it can be beneficial in the clinical assessment.

Genetic studies

The pathological etiology of Laron-type dwarfism is related to the GH receptor and its coding gene. GH receptor gene is an 87 kilobase-transmembrane protein from the cytokine receptor family and is encoded by ten exons. The receptor consists of three domains: extracellular, transmembrane and intracytoplasmic domains. Exons 2–7 encode the first, exon 8 encodes the second and exons 9–10 encode the third domain. Based on the affected exon, deletions, nonsense, missense, splice and frameshift point mutations in the GH receptor gene, may lead to GH resistance by interfering with receptor functions. The most important mutations are the surface receptor mutations connected with the extracellular domain [3, 13, 28–32].

Treatment of the Laron-type dwarfism

Recombinant human IGF-1 preparations (rhIGF-1, mecasermin) are used in the treatment of the Classic Laron syndrome as well as in the mutations of the GH–GH receptor activation pathway and in the presence of the growth hormone inhibiting antibody. The brand name of the preparation is "Increlex". Increlex is available in 4 ml-vials containing 40 mg of rhIGF-1. The recommended dose is 40–120 μg/kg given subcutaneously twice daily [2]. The starting dose is recommended as 40–80 μg/kg twice daily by the subcutaneous route. If the dose is well tolerated during the first week, the dose is increased 40 μg for each application and the maximum dose should not exceed 120 μg/kg. The height growth increases from 2.9–0.6 to 8.8–0.6 cm/year with treatment [4]. Laron et al. [33] reported that; there were no significant difference of growth velocity between the injection forms neither once nor twice in a day. Therefore, once a day administration of IGF-1 is recommended and found as effective as the two doses/day. Ranke et al. provided an improvement of 1.7–1.2 SD in the height SD score using IGF-I treatment at the age of nine, in 31 Laron-typed dwarfs and recommended early initiation of the treatment [34]. Camacho-Hübner et al. investigated rhIGF-1/rhIGFBP-3, a 1:1 molar complex of rhIGF-1 and rhIGFBP-3 as alternative treatment. The complex was effective in increasing total and free IGF-1 levels after a single subcutaneous administration. Additionally it was safe and well tolerated without acute insulin side effects associated with IGF-1 therapy [35].

The treatment leads to increases in the annual height growth, improvements in the dysmorphic facial features along with the anabolizing and lipolytic effects and positive impacts on the musculoskeletal mass. The response to treatment may be more impressive in patients with severe phenotypical findings, since the phenotypical features of the patients reflect the disease severity. In spite of the acceleration in growth, the height still remains below the third percentile in most of the cases. IGF-1 treatment is considered to exert endocrine effects, but not paracrine or autocrine effects. The response to treatment is limited during puberty. The adverse effects of the IGF-1 treatment include intracranial hypertension (5 %), headache and transient papilledema. Other adverse effects are lipohypertrophy and pain at the injection site, similar to insulin. These side effects may occur

in 33 % of the cases and may be prevented by the frequent change of the injection sites. Lymphoid tissue hyperplasia including tonsillar and adenoid hyperplasia in 25 % of the cases (10 % of the patients require surgery), recurrent otitis, snoring and sleep apnea may occur. Of the lymphoid organs, thymus and spleen may also be enlarged [4]. Furthermore, gastroenteritis, vomiting, anaphylaxis, asymptomatic tachycardia and increased transaminase levels have been reported. Overdose may result in the signs of hyperandrogenism. One of the important adverse effects is hypoglycemia [2, 36]. Hypoglycemia has been reported in 8 % of the cases [2]. Hypoglycemia is more prevalent during the first month of the treatment. Inadequate nutrition and excessive exercising within 2–3 h after the injection may increase the risk of hypoglycemia. Patients are recommended not to skip any main meals or refreshments. The dose should be reduced in patients with low blood glucose levels in spite of adequate nutrition. Significant changes may be observed in the facial appearance during the treatment. Facial appearance may become more mature due to the facial elongation as a result of endochondral bone growth. Meanwhile, pronounced supraorbital ridges and thickened lips and nose may result in a coarse facial appearance similar to acromegaly [19]. Another risk in these patients is the increase in the body mass index (BMI). GH therapy leads to a reduction in the body fat ratio. On the other hand IGF-1 therapy increases both fatty tissue and lean body mass. An increase of 0.6–1.8 SD in the BMI after 4–7 years of treatment was demonstrated in a multicenter study conducted in Europe [4]. There are no definite data on whether the long-term use of the medicine is associated with a mitogenic (anti-apoptotic) effect. Therefore, it should not be used in patients with a tendency to develop malignancy. Although anti-IGF antibodies have been observed in 50 % of the patients, during the first year of treatment, any negative impact on the response to treatment was observed in such cases [4].

Long-term problems in Laron-type dwarfs

The final height in boys with Laron syndrome ranges between 119 and 142 cm while the final height ranges between 108 and 136 cm in girls. The height deficit varies from −4 to −8 height SDs [10]. The patients with Laron are obese during the childhood and obesity increases with age. Actually, fat tissue increases in these patients despite insufficient muscle mass. The closure of the cranial fontanel and sutures is delayed and osteoporosis occurs in early adulthood. The deficits in performance IQ are more prominent than those of verbal IQ. While low IQ score is more prevalent among Jewish patients, it is rarely reported in Ecuadorian cases. Verbal IQ improves with age. The delay in the onset of puberty is more prominent among males and the cases do not experience an actual pubertal height growth spurt. However, both genders experience a full sexual development [10].

Growth hormone signal transduction abnormalities

STAT5b deficiency

To date, only six cases with growth failure have been identified as STAT5b genetic abnormalities. Their birth sizes are normal or slightly reduced and postnatal growth is poor. Heights have ranged from −5.6 to −9.9 SD. Their laboratory results showed a marked reduction in serum IGF-1, IGFBP-3 and ALS levels. Although there was little increase seen in the serum IGF-1 concentration, after GH administration; there weren't any reported growth acceleration. The patients carrying STAT5b mutation present with a history of immunological dysfunction. Their features include chronic pulmonary disease and life-threatening infections such as chronic diarrhea, severe eczema, herpes keratitis, herpes zoster, severe varicella and juvenile arthritis [37, 38].

Primary defect of IGF-1 synthesis (IGF-1 gene mutation), IGF-1 receptor deficiency, bioinactive IGF-1, IGFBP-3/acid labile subunit (ALS) mutation

Primary defect of IGF-1 synthesis

In 1996, Wood et al. [39] detected deletions in 2 of 6 exons in a case of severe postnatal growth failure with prenatal onset. The case presented with microcephaly, mental retardation and sensorineural hearing loss. The absence of prenatal growth retardation and mental retardation in GH deficiency supports the role of IGF-1 deficiency in the case. The features of IGF-1 deficiency are extremely short stature (-3 SDS), high GH levels and very low IGF-1 levels (-3SDS), normal IGF-BP3 levels and IGF-II levels higher than normal along with mildly delayed bone age. Hypoglycemia is not a feature of IGF-1 deficiency.

IGF-1 receptor deficiency

Receptor defects leading to severe intrauterine growth retardation and central nervous system malformations in animal studies have not been accurately determined in humans. However, high GH and IGF-1 levels were observed in a few cases and impaired receptor binding of IGF-I was demonstrated in fibroblast cell cultures [38].

Bioinactive IGF-1

This situation is similar with IGF-1 receptor defect. Both intrauterine and postnatal severe growth retardation are associated with bioinactive IGF-1. These patients have

elevated levels of IGF-1 and under feedback from increased GH secretion, expressed at increased levels [40, 41].

Acid-labile subunit (ALS) deficiency

This situation was described in 2004. The main function of ALS is to constitute the IGF-1, IGFBP-3/IGFBP-5 complexes and prolong half-life. Generally, patients with ALS present with delayed onset of puberty and slow pubertal progress. Although both serum IGF-I and IGFBP-3 concentrations are significantly reduced, growth retardation is surprisingly modestly affected. Serum IGFBP-3 levels are more markedly affected than IGF-1. Insulin insensitivity and reduction in bone mineral density are also other findings. ALS is undetected in the serum before and after GH [42, 43].

Other conditions

Kowarski syndrome

This syndrome was first published in 1978 as a new growth disorder in two boys at the age of 3, presenting with growth retardation, delayed bone age, low IGF-1 levels and adequate response to GH stimulation test. Exogenous growth hormone administration led to the increased IGF-1 levels and accelerated growth in the cases. The GH type in these patients was found to be biologically inactive and this hormone was defined as bio-inactive growth hormone [44].

Secondary growth hormone resistance (insensitivity) disorders

Antibodies against growth hormone

In patients treated with rhGH, immunological reactions may occur during and after treatment. Antibody against rhGH can neutralize circulating growth hormone effects. GH antibodies have no negative effect on height and growth velocity as well as height standard deviation score of growth hormone deficiency children. Moreover, after stopping rhGH treatment or changing to preparation, the GH antibodies disappear rapidly in most patients [45, 46].

Antibodies against growth hormone receptor

The GH receptor contains an extracellular domain including hormone-binding site and soluble binding protein, a single transmembrane domain and an intracellular region. Antibodies occur against the extracellular domain and soluble binding protein. Various antibodies have different effects on receptor as GH antagonist or agonist [47, 48].

Insensitivity to growth hormone in cases of malnutrition, inflammatory bowel disease, severe disease and catabolic state

In these conditions, growth may be affected from mild to moderate. Laboratory findings include high GH, variable IGF-1, low GHBP and low or normal IGFBP-3 levels. Also, there are typical findings of the main diseases [49].

Insensitivity to growth hormone in liver diseases

Alagille syndrome is a prototype in this situation. Alagille syndrome is inherited in an autosomal dominant trait pattern and the condition may affect the liver, heart, eyes, spine, face and kidneys [1, 50]. Chronic cholestasis beginning at birth is the most prominent characteristic of the disease. This aspect of the disease can make it difficult to distinguish from biliary atresia. Cardiac murmur, posterior embryotoxon, butterfly vertebra, renal malformations and typical facial appearance are seen. The facial features include prominent forehead, deep-set eye, mild hypertelorism, bulbous nose and triangular face shape. The ears are prominent and flat. Micropenis, empty scrotum and gallstones may be detected in certain cases. The most important endocrine findings are the elevated GH and low IGF-1 levels. Liver biopsy may reveal the scarcity of interlobular bile ducts [50].

Insensitivity to growth hormone in poorly controlled diabetes

Insulin dependent diabetes mellitus causes hepatic GH resistance. As a result, circulating IGF-1 levels decrease. Lack of the negative feedback effect causes GH hyper secretion. IGFBP-3 levels increase and GHBP decreases. Growth failure in type 1 diabetes can occur mild or severe as called Mauriac syndrome. Mauriac syndrome is characterized by hepatomegaly, growth retardation and cushingoid features [51].

Other conditions

Idiopathic short stature

The term of "idiopathic short stature" is used for the children who are below 2 SD in height SD scores, below 2 SD or normal in bone age, or below the 25th percentile in the growth rate, in spite of a normal birth weight and the absence of any endocrine disorder or any chronic physical or psychological problem [52]. The karyotype is normal and the head circumference, upper-to-lower body segment ratio, sitting height and arm span length are within normal limits in the cases of idiopathic short stature.

Clonidine and arginine stimulation tests reveal a normal GH level, while IGF-1 levels are low or normal (25 %). The GHBP has been found to be decreased in 20 % of the cases. Heterozygous mutations in the GH receptor gene were detected in 5 % of the patients with the diagnosis of idiopathic short stature. Certain investigators have suggested that these cases might be a mild form of the Laron syndrome. Therefore, a possible partial GH receptor resistance should be kept in mind in cases of idiopathic short stature. Furthermore, SHOX gene mutations have been demonstrated in 1–5 % of the cases. On the other hand, polymorphisms have been demonstrated on 10th intracellular exon of GH receptor gene, in some cases [53].

Turner and Noonan syndrome

Various abnormalities in the GH/IGF-I axis and in the synthesis, secretion and biologic effects of GH that become prominent, particularly in the puberty years, have been demonstrated in cases of Turner syndrome [54]. Similarly, about half of the cases of Noonan syndrome exhibit heterozygous mutations in the non-receptor-type tyrosine phosphatase gene (PTPN11) that has a role in GH receptor signaling [55]. A post-receptor signaling defect and a mild GH resistance are observed in Noonan syndrome as a result of this mutation. Although it is partial, this defect may be compensated by the increased level of GH.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent There is no informed consent.

References

1. Chernausek SD, Horn JA (1998) Growth hormone resistance: biologic implications. J Endocrinol Invest 21:18–23
2. Richmond EJ, Rogol AD (2008) Recombinant human insulin-like growth factor-1 therapy for children with growth disorders. Adv Ther 25:1276–1287
3. Rosenbloom AL (1999) Growth hormone insensitivity: physiologic and genetic basis, phenotype, and treatment. J Pediatr 135:280–289
4. Rosenbloom AL (2009) Mecasermin (Recombinant human insulin-like growth factor 1). Adv Ther 26:40–54
5. Laron Z, Pettzelan A, Mannheimer S (1966) Genetic pituitary dwarfism with high serum concentration of growth hormone. A new inborn error of metabolism? Isr J Med Sci 2:152–155
6. Laron Z (1999) Natural hystory of the classical form of primary growth hormone resistance (Laron syndrome). JPEM 12:231–249
7. Johnson LB, Woods KA, Rose SJ, Clark AJL, Savage MO (1998) The broad spectrum of inherited growth hormone insensitivity syndrome. TEM 9:228–232
8. Yordam N, Kandemir N, Erkul I, Kurtoglu S, Hatun S (1995) Review of Turkish patients with growth hormone insensitivity (Laron type). Eur J Endocrinol 133:539–542
9. Domone HM, Bengolea SV, Jasper HG, Boisclair YR (2005) Acid-labile subunit deficiency: phenotypic similarities and differences between human and Mouse. J Endocrinol Invest 28(Suppl 5):43–46
10. Laron Z, Blum W, Chatelain P, Ranke M, Rosenfold R, Savage M, Underwood L (1993) Classification of growth hormone insensitivity syndrome. J Pediatr 122:241
11. David A, Hwa V, Metherell LA et al (2011) Evidence for a continuum of genetic, phenotypic, and biochemical abnormalities in children with growth hormone insensitivity. Endocr Rev 32:472–497
12. Laron Z, Ginsberg S, Lilos P, Arbiv M, Vaisman N (2006) Body composition in untreated adult patients with Laron syndrome (primary GH insensitivity). Clin Endocrinol Oxf 65:114–117
13. Burren CP, Woods KA, Rose SJ et al (2001) Clinical and endocrine characteristics in atypical and classical growth hormone insensitivity. Horm Res 55:125–130
14. David A, Metherell LA, Clark AJL, Camacho-Hübner C, Savage MO (2005) Diagnostic and therapeutic advances in growth hormone insensitivity. Endocrinol Metab Clin N Am 34:581–595
15. Johnston LB, Savage MO (1999) Partial growth hormone insensitivity. JPEM 12:251–257
16. Backeljauw PF, Chernausek SD (2012) The insulin-like growth factors and growth disorders of childhood. Endocrinol Metab Clin N Am 41:265–282
17. Blum WF, Cotterill AM, Postelninay MC, Ranke MB, Savage MO, Witon P (1994) Improvement of diagnosis criteria in growth hormone insensitivity syndrome: solutions and pitfalls. Acta Paediatr Suppl 399:117–124
18. Marzullo P, Buckway C, Pratt KL, Colao A, Guevara-Aguirre J, Rosenfeld RG (2002) Leptin concentrations in GH deficiency: the effect of GH insensitivity. J Clin Endocrinol Metab 87:540–545
19. Spiliotis BE, Alexandries TK, Karystianos C et al (2009) The insulin-like growth factor-1 (IGF-1) generation test as an indicator of growth hormone status. Hormones 8:117–128
20. Rudman D, Kutner MH, Blackston RD, Cushman RA, Bain RP, Patterson JH (1981) Children with normal-variant short stature: treatment with human growth hormone for six months. N Eng J Med 305:123–131
21. Darendeliler F, Ocal C, Bas F (2005) Evaluation of insulin-like factor (IGF-1) and IGF binding protein-3 generation test in short stature. JPEM 18:443–452
22. Cotterill AM, Camacho-Hubner C, Woods K, Martinelli C, Duqesnoy P, Savage MO (1994) The insulin-like growth factor-1 generation test in the investigation of short stature. Acta Paediatr Suppl 399:128–130
23. Chyrsis DC, Alexandrides TK, Koromantzou E et al (2001) Novel application of IGF-1 and IGFBP-3 generation tests in the diagnosis of growth hormone axis disturbances in children with beta-thalassemia. Clin Endocrinol 54:253–259
24. Buckway CK, Guevara-Aguirre J, Pratt KL, Burren CP, Rosenfeld RG (2001) The IGF-1 generation test revisited: a marker of growth hormone insensitivity. JCEM 86:5176–5183
25. Buckway CK, Selva KA, Pratt KL, Tjoeng E, Guevara-Aguirre J, Rosenfeld RG (2002) Insulin-like factor binding protein-3 generation as a measure of growth hormone insensitivity. JCEM 87:4754–4765
26. Turan S, Bereket A, Furman A et al (2007) The effect of economic status on height, insulin-like growth factor (IGF)-I and

IGF binding protein-3 concentrations in healthy Turkish children. Eur J Clin Nutr 61:752–758
27. Coutant R, Dörr HG, Gleeson H, Argente J (2012) Limitations of the IGF1 generation test in children with short stature. Eur J Endocrinol 166:351–357
28. Arman A, Ozon A, Isguven PS, Coker A, Peker I, Yordam N (2008) Novel slice site mutation in the growth hormone receptor gene in Turkish patients with Laron-type dwarfism. JPEM 21:47–58
29. Bonioli E, Taro M, LaRosa G et al (2005) Heterozygos mutations of growth hormone receptor gene in children with idiopathic short stature. Growth Hormon IGF Res 15:405–410
30. Sobrier ML, Dastot F, Duguesnoy P et al (1997) Nine novel growth hormone receptor gene mutations in patients with Laron syndrome. JCEM 82:435–437
31. Wit JM, van Duyvenvoorde HA, Scheltinga SA et al (2012) Genetic analysis of short children with apparent growth hormone insensitivity. Horm Res Paediatr 77:320–333
32. Savage MO, Hwa V, David A, Rosenfeld RG, Metherell LA (2011) Genetic defects in the growth hormone-IGF-1 axis causing growth hormone insensitivity and impaired lineer growth. Front Endocrinol 2:1–12
33. Laron Z (2013) If one daily injection of IGF-I has the same growth-promoting effect as 2 injections per day, why continue to give two injections? Pediatr Endocrinol Rev 10:277–279
34. Ranke MB, Savage MO, Chatelain PG, Preece MA, Rosenfeld RG, Wilton P (1999) Long term traetment of GHIS with IGF-1. Results of the European multicenter study. Horm Res 51:128–134
35. Camacho-Hübner C, Rose S, Preece MA, Sleevi M, Storr HL et al (2006) Pharmacokinetic studies of recombinant human insulin-like growth factor I (rhIGF-I)/rhIGF-binding protein-3 complex administered to patients with growth hormone insensitivity syndrome. J Clin Endocrinol Metab 91:1246–1253
36. Balhara B, Misra M, Levitsky LL (2012) Recombinant human IGF-1 (Insulin-like growth factor) therapy: where do we stand today? Indian J Pediatr 79:244–249
37. Hwa V, Nadeau K, Wit JM, Rosenfeld RG (2011) STAT5b deficiency: lessons from STAT5b gene mutations. Best Pract Res Clin Endocrinol Metab 25:61–75
38. Rosenfeld RG, Belgorosky A, Camacho-Hubner C, Savage MO, Wit JM, Hwa V (2007) Defects in growth hormone receptor signaling. Trends Endocrinol Metab 18:134–141
39. Woods KA, Camacho-Hübner C, Savage MO, Clark AJL (1996) Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor 1 gene. N Eng J Med 335:1363–1367
40. Saenger P, Czernichow P, Hughes I, Reiter EO (2007) Small for gestational age: Short stature and beyond. Endocr Rev 28:219–251
41. Chernausek SD (2006) Mendelian genetic causes of the short child born small for gestational age. J Endocrinol Invest 29:16–20
42. Domené HM, Bengolea SV, Martínez AS (2004) Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene. N Engl J Med 350:570–577
43. Domené HM, Hwa V, Jasper HG, Rosenfeld RG (2011) Acid-labile subunit (ALS) deficiency. Best Pract Res Clin Endocrinol Metab 25:101–113
44. Kowarski AA, Schneider J, Ben-Galim E, Weldon VV, Daughaday WH (1978) Growth failure with normal serum RIA-GH and low somatomedin activity: somatomedin restoration and growth acceleration after exogenous GH. J Clin Endocrinol Metab 47:461–464
45. Ahangari G, Ostadali MR, Rabani A, Rashidian J, Sanati MH, Zarindast MR (2004) Growth hormone antibodies formation in patients treated with recombinant human growth hormone. Int J Immunopathol Pharmacol 17:33–38
46. Massa G, Vanderschueren-Lodeweyckx M, Bouillon R (1993) Five-year follow-up of growth hormone antibodies in growth hormone deficient children treated with recombinant human growth hormone. Clin Endocrinol Oxf 38:137–142
47. Lan H, Li W, Fu Z et al (2014) Differential intracellular signalling properties of the growth hormone receptor induced by the activation of an anti-GHR antibody. Mol Cell Endocrinol 390:54–64
48. Lattuada D, Casnici C, Perego C et al (2000) Monoclonal antibody against human growth hormone receptor. Hybridoma 19:177–183
49. Cappa M, Loche S (2003) Evaluation of growth disorders in the paediatric clinic. J Endocrinol Invest 26(7 Suppl):54–63
50. Alagille D, Odievre M, Gautier M, Dommergues JP (1975) Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac failure. J Pediatr 86:63–71
51. Kim MS, Quintos JB (2008) Mauriac syndrome: growth failure and type 1 diabetes mellitus. Pediatr Endocrinol Rev 5:989–993
52. Ranke MB (1996) Towards a concensus on the definition of idiopathic short stature. Horm Res 45(Suppl 2):64–66
53. Attie KM (2000) Genetic studies in idiopathic short stature. Curr Opin Pediatr 12:400–404
54. Kiess W, Kratzsch J, Pfaeffle R (2006) The growth hormone and insulin-like growth factor system in girls and women with Turner syndrome. Int Congr Series 1298:63–70
55. Binder G, Neuer K, Ranke MB, Wittekindt NE (2005) PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. JCEM 90:5377–5381