



Review

Isolated Growth Hormone Deficiency

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Abstract: Growth hormone deficiency (GHD) is the most frequent pituitary hormone deficiency in childhood, with an incidence of 1 in 4000–10,000 live births. GHD can be congenital (genetic or due to hypothalamic/pituitary abnormalities) or acquired and can be isolated (IGHD) or associated with other pituitary hormone deficiencies, but most cases are idiopathic. GH stimulation testing is commonly used in the diagnostic workup of GHD, except for some clinical conditions that do not require GH stimulation tests for the diagnosis. Children with GHD receive replacement therapy with daily injections of recombinant human GH (rhGH). RhGH therapy is effective in increasing short-term height gain and adult height in patients with GHD. The safety of long term GH therapy has been confirmed in many large international studies. Recently, long-acting weekly GH formulations have been introduced, showing good efficacy and safety profiles.

Keywords: growth hormone deficiency; pediatric; growth hormone stimulation test; children; recombinant growth hormone



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1. Introduction

Isolated growth hormone deficiency (IGHD) is the commonest pituitary hormone deficiency, with an incidence of 1 in 4000 to 10,000 live births. In 3–30% of cases, IGHG is familial, whereas the majority of cases are idiopathic. IGHG can be present from the first years of life (congenital); secondary to autoimmune disease, brain trauma or infections, tumors or radiotherapy (acquired); or idiopathic.

Congenital IGHG can be secondary to genetic mutations in the gene encoding growth hormone (*GH1*) or the gene encoding the growth hormone releasing hormone receptor (*GHRHR*) [1–3]. Dominant or recessive pathogenic variants in the genes encoding transcription factors involved in the embryonic development of the pituitary such as *PROP1*, *HESX1*, *SOX3*, *OTX2*, *GLI2*, *LHX3*, *LHX4* and *POU1F1* [4,5] usually cause progressive multiple pituitary hormone deficiency (MPHD) but may occasionally cause IGHG [1,2,6].

The clinical phenotype of GHD varies depending on the age of presentation. Jaundice, hypoglycemia and/or underdeveloped male genitalia may be signs of neonatal GHD, whereas short stature and/or decreased growth velocity and delayed bone age may be the first signs in older children [7].

Since GH production is pulsatile, baseline GH measurement is useless, and assessment of its secretion requires stimulation testing. Although some authors have suggested that GH stimulation tests (GHSTs) are not always necessary for the diagnosis of GHD [8–10], they are still recommended by the most recent guidelines in children and adolescents with suspected GHD [11,12]. However, the accuracy of GHSTs is still matter of debate due to the arbitrarily established cut-off, non-physiological test procedures, variability in the type of stimulation test and type of assay and the influence of factors such as obesity

or undernutrition. The decision to perform GHSTs should be based on clinical findings and biochemical results such as low insulin-like growth factor 1 (IGF-1) and IGF binding protein-3 (IGFBP-3). Moreover, in prepubertal boys older than 11 years and girls older than 10 years, priming with sex steroids before testing is recommended to avoid false positive results.

When GHD is confirmed, brain magnetic resonance imaging (MRI) studies should always be performed to evaluate the anatomy of the hypothalamic–pituitary area and to exclude a possible organic cause of GHD such as tumors (e.g., craniopharyngioma or germinoma) [12–14].

Neonates and infants with clinical signs of GHD associated with low IGF-1 and IGFBP-3, MPHD and/or abnormalities on brain MRI do not need GHSTs for diagnosis [15–17].

In this review, we summarize the current evidence on the causes, diagnosis and treatment of IGHD in the pediatric population.

2. Physiopathology

GH secretion is mainly regulated by the coordinate and opposite action of hypothalamic GHRH and somatostatin, which, respectively, stimulate and inhibit its release from the pituitary somatotrophs. Other hormones are also involved in the regulation of GH synthesis and secretion, including glucocorticoids, ghrelin, IGF-1, thyroid hormone and gonadal steroids. GH levels are high and pulsatile at birth and in the first week of life [7] and rapidly decrease during the following weeks. GH secretion is also influenced by exercise, chronic malnutrition, trauma, chronic kidney disease and sepsis [18]. GH has multiple actions that include increasing muscle mass, and regulating lipid and carbohydrate metabolism and body water throughout life, but in neonates specifically, it is essential for glucose and fat metabolism [7,19], whereas it primarily stimulates bone growth and density in children and adolescents. The main effector of GH is IGF-1 [5], which is mostly secreted by the liver and circulates coupled to specific binding proteins (IGFBPs 1–6), mainly IGFBP-3. Several factors and hormones such as malnutrition or anorexia nervosa, thyroid hormone, estrogens and androgens, chronic diseases and inflammation may influence IGF-1 production and action [20–24]. For the first 15–18 months of age, serum IGF-1 concentrations are low, after which they start to increase until a pubertal peak and decrease thereafter [25,26].

3. Diagnosis of IGHD

3.1. Clinical Presentation

3.1.1. Newborn

GHD in neonates often presents as MPHD but can also be isolated. Its causes include congenital abnormalities of the hypothalamic–pituitary region, midline defects and genetic abnormalities. The severity of the clinical presentation depends on the number of affected hormones and may vary from non-specific symptoms and signs, such as lethargy and poor weight gain, to life-threatening episodes [27]. Intrauterine growth is generally normal, although birth length can be slightly reduced. Physical findings such as midface hypoplasia and frontal bossing, eye abnormalities, microphallus and a single central maxillary incisor can suggest the presence of GHD.

3.1.2. Infant/Child

Most cases of IGHD in childhood are idiopathic. Short stature is the typical clinical presentation of GHD in infancy and childhood and is defined as height more than 2 SD below the population mean. Growth arrest or height velocity deceleration with normal/increased weight and delayed skeletal maturation are commonly associated. A child with GHD may present with an immature appearance, midface hypoplasia, frontal bossing, a depressed nasal bridge, delayed dentition and truncal adiposity. Micropenis may be associated and suggests a congenital form.

The presence of a pituitary mass, brain tumors, or the presence of infections of central nervous system should always be ruled out at any age. Furthermore, GHD should be

suspected in all short children who have received cranial irradiation [28,29] or suffered brain injuries [30].

3.2. Laboratory

3.2.1. Newborn

In the neonatal period, a single GH measurement is usually sufficient to confirm the diagnosis of GHD [31,32] without the use of GHSTs [10,25,33]. The clinical suspicion of neonatal GHD can be confirmed by low baseline GH concentrations, preferably obtained during hypoglycemic episodes [33]. Various cut-offs for the diagnosis of neonatal GHD have been proposed, ranging from 7 to 20 µg/L [11,25]. Furthermore, serum GH concentrations ≤ 5 ng/mL associated with other pituitary hormone deficiencies or/and the triad of pituitary hypoplasia, ectopic posterior pituitary and abnormal pituitary stalk is strongly suggestive of GHD according to the current guidelines. Furthermore, Binder et al. [33] measured GH concentrations on newborn screening cards and demonstrated that GH concentration < 7 µg/L in term newborns with a specific phenotype (recurrent hypoglycemia, other pituitary hormone deficiencies and/or a significant pituitary malformation on brain MRI) confirms severe GHD with high reliability. However, the accuracy of newborn screening cards in the diagnosis of GHD has not been confirmed yet [34].

3.2.2. Infant/Child

GHSTs are still considered the gold standard test for the diagnosis of GHD in childhood [12,35–38]. Traditionally, a lack of response to two different GHSTs in a patient with short stature with normal body proportion, reduced height velocity, delayed bone age and eventual positive medical history confirms GHD.

A large number of GHSTs have been proposed, used and studied in the last few decades [11,16,39–41]. Nonetheless, GHSTs are still considered to have poor specificity and reproducibility [40] in addition to being clearly non-physiological. Furthermore, the diagnostic cut-offs used worldwide are still arbitrarily established by individual centers or decided by national scientific associations or societies, ranging from 3 to 10 µg/L [11,12,16,36,40,42–45]. Furthermore, GHSTs have been shown to be even less accurate in children younger than 4 years, and the increased occurrence of side effects is a further limitation to their use [15,40]. It should be pointed out that GH secretion is also influenced by body mass index, undernutrition and puberty, but no specific cut-off for any condition has been established [46–50]. However, in the presence of auxological findings suggestive of GHD, hypothalamic–pituitary defects (congenital or acquired) and one additional pituitary hormone deficiency, GHSTs are not necessary for the diagnosis of GHD [10,12,28,29]. Due to the low reliability of GHSTs, alternative diagnostic strategies such as measurement of IGF-1 and IGFBP-3, genetic testing and brain MRI have been considered over the years for support in the diagnostic workup process [8,9,15,51].

3.3. IGF-1 and IGFBP-3

Measurement of IGF-1 alone is considered not to be useful for the diagnosis of IGHD [52]. Its usefulness for the diagnosis of GHD in children has been evaluated in a number of studies [12,23,37,39,42,43,49,51,53–60]. Together, these studies have shown that IGF-1 measurement has poor sensitivity and specificity. IGF-1 concentrations are low in neonates and during the first 15–18 months of age [25,26]. Thus, IGF-1 is considered useful only when combined with clinical and auxological parameters and the results of GH stimulation testing [43,51,52,54,56,61,62]. Furthermore, age, gender, pubertal status and body mass index should be considered when interpreting the results of IGF-1 measurement [23]. Therefore, IGF-1 concentrations overlap between GHD and non-GHD subjects, and very low levels (<−2 SDS) strongly suggest the presence of GHD, but normal IGF-1 concentrations do not exclude GHD at any age [63]. Interestingly, Wit et al. [23] proposed a method to estimate the probability of GHD in a child with growth failure using IGF-1 measurement, determining the pre- and post-test likelihood.

IGFBP-3 levels is less influenced by nutrition than IGF-1, and it is considered more useful in patients under 3 years of age [56,64].

3.4. Magnetic Resonance Imaging

The diagnostic accuracy and the widespread use of MRI have led to a significant increase in our knowledge of pituitary morphology and function, which has expanded the landscape of the differential causes of GHD [65–67]. Current guidelines [16] still recommend performing a brain MRI after the diagnosis of GHD is confirmed. Pituitary hypoplasia is the most frequent abnormality [68]. Other, less common abnormalities include pituitary stalk interruption syndrome (PSIS) [69] and ectopic posterior pituitary. It should be pointed out that the presence of a reduced pituitary gland volume alone is not sufficient to make the diagnosis of GHD but is an indication that further evaluation of pituitary function is needed [16]. There has been a proposal to perform brain MRI as a first-line investigation [15] in children younger than 4 years of age, eventually followed by GHSTs later in life, when they can be more easily performed.

3.5. Genetic Testing

Genetic testing is indicated in the presence of a positive family history, anatomic anomalies or extreme short stature [16].

Pathogenic variants in the *GH1* and *GHRHR* genes are the most frequent genetic abnormalities in patients with IGHD and may be associated with normal MRI [1,3,4,70,71]. The clinical phenotype of IGHD correlates with the severity of the mutation. IGHD type IA is due to homozygous deletion of the *GH1* gene. The phenotype is characterized by early, severe short stature (height < −4.5 SDS), undetectable GH concentrations and tachyphylaxis to GH treatment due to the formation of GH antibodies [72,73]. IGHD type IB can be due to recessive *GH1* mutations and presents milder growth failure, low but detectable GH concentrations and a good response to treatment [3]. IGHD type II, the commonest form, is autosomal dominant; it can present with a variable phenotype with detectable GH concentrations, and patients can develop other pituitary hormone deficiencies over time [71,74], as well as occasional anterior pituitary hypoplasia [75,76]. IGHD type III is X-linked and is caused by mutations in the *SOX3* or *BTK* gene [77,78]. The phenotype can present with IGHD or MPHD with or without an ectopic posterior pituitary, intellectual disability and abnormal immune function [77,78]. IGHD type IV is caused by homozygous or compound heterozygous mutations in the *GHRHR* gene. The phenotype is characterized by the presence of pituitary hypoplasia, severe short stature, extremely low baseline and stimulated GH concentrations, low concentrations of IGF-1 and IGFBP-3 and a good response to GH replacement therapy [79,80]. IGHD type V is due to recessive mutations in the RNA Binding Region (RNP1, RRM) containing 3 (*RNPC3*) gene that cause severe postnatal growth retardation, undetectable baseline and stimulated GH concentrations, low to undetectable IGF-1 and IGFBP-3 concentrations, low to normal prolactin concentrations and anterior pituitary hypoplasia [81]. Female patients with mutations in the *RNPC3* gene can also develop ovarian insufficiency. Less frequently, IGHD can be caused by mutations in the GH secretagogue receptor (*GHSR*) gene [82,83]. The genotype–phenotype correlations of the different genetic IGHD types are summarized in Table 1.

Table 1. Description of the different types of genetic IGHD. AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

IGHD Type	Gene/Chromosome	Inheritance	Phenotype	Response to Treatment
IA	<i>GH1</i> /17q23.3	AR	Early, severe short stature (height < −4.5 SDS); undetectable GH concentrations	Tachyphylaxis to GH
IB	<i>GH1</i> /17q23.3	AR	Milder growth failure, low but detectable GH concentrations	Good

Table 1. Cont.

IGHD Type	Gene/Chromosome	Inheritance	Phenotype	Response to Treatment
II	<i>GH1</i> /17q23.3	AD	Variable phenotype, detectable GH concentrations, possibility of other pituitary hormone deficiencies, occasional anterior pituitary hypoplasia	Good
III	<i>SOX3</i> or <i>BTK</i> /Xq22.1	XL	IGHD or MPHD with/without an ectopic posterior pituitary, intellectual disability and abnormal immune function, agammaglobulinemia	Good
IV	<i>GHRHR</i> /7p14.3	AR	Pituitary hypoplasia, severe short stature, extremely low baseline and stimulated GH concentrations, low concentrations of IGF1 and IGFBP3	Good
V	<i>RNPC3</i> /1p21.1	AR	Severe postnatal growth retardation, undetectable baseline and stimulated GH concentrations, low to undetectable IGF-1 and IGFBP-3 concentrations, low to normal prolactin concentrations, anterior pituitary hypoplasia, ovarian insufficiency	Good

Mutations in a number of other genes encoding transcription factors involved in all the steps of the embryonic development of the pituitary gland (i.e., *POU1F1*, *PROP1*, *LHX3*, *LHX4*, *HESX1*, *SOX2*, *SOX3*, etc.) are generally associated with MPHD, and most of them are associated with some typical clinical and neuro-radiological features.

4. Treatment and Outcome

Recombinant human growth hormone (rhGH) has been used to treat patients with GHD since 1985 [84]. Before that date, patients were treated with GH extracted from cadaveric pituitary glands, putting patients at risk of Creutzfeldt–Jakob disease after up to 40 years. From 1985, the availability of unlimited rhGH made it possible to improve treatment strategies to maximize the efficacy of therapy.

Normalization of the growth rate and the achievement of a normal adult stature are the primary goal of rhGH therapy. In addition, GH treatment is important for its effects on metabolism and body composition. In fact, rhGH therapy improves body composition, reducing body fat and increasing fat-free mass (including bones and muscles). Furthermore, rhGH antagonizes the effects of insulin, with consequent stimulation of lipolysis, and exerts important effects on bone metabolism (i.e., promotion of skeletal IGF-1 synthesis, proliferation of prechondrocytes with stimulation of cartilage growth and hypertrophy of osteoblasts with bone remodeling and improved mineralization) [85]. RhGH is classically administered daily (six or seven days/week). The subcutaneous injections should be given at night (in order to mimic the physiological GH secretory pattern) with an easy-to-use multiple-dose pen or similar devices [12]. GHD patients receiving rhGH should be evaluated every 3 to 6 months. The initial suggested dose is 22–35 µg/kg/day (0.16–0.24 mg/kg/week), with subsequent individualization according to body weight, height velocity and IGF-1 concentrations [12,14]. Most pediatric endocrinologists suggest starting at the lower end of the dose range and then titrating according to the patient's response. It is not recommended to routinely increase the dose during puberty [12].

IGF-1 serum levels should be maintained within the normal range for the patient's age and sex to avoid over- or under-treatment. Epidemiological studies indicate that chronically elevated IGF-1 serum levels may be associated with the development of tumors in adulthood. However, a causal relationship between supra-physiological IGF-1 levels during rhGH treatment and tumor formation or progression has never been demonstrated.

GH affects both thyroxine and cortisol catabolism: the first due to an increase in peripheral conversion of T4 to T3, and cortisol catabolism due to the inhibition of 11βHSD1 in the conversion of cortisone to cortisol, thereby unraveling central hypothyroidism or hypoadrenalism [86–88]. For these reasons, adrenal and thyroid function should be periodically evaluated during rhGH treatment.

4.1. Efficacy

Pediatric rhGH therapy increases short-term height gain and adult final height in patients with IGHD [89]. However, the response to rhGH therapy is variable between patients, and this variability can be due to a number of factors including the duration of treatment, patient sensitivity to rhGH, dose, bone age, severity of GHD, adherence to treatment and the development of GH antibodies [90–94]. RhGH responsiveness may be indicated by the growth response during the first year of therapy, although there is not a universal definition of what can be considered a “good” response. For example, it has been suggested that HV below -1 SD during the first year of treatment according to age- and gender-specific targets may be considered a “poor” response [91]. Height SDS improvement lower than 0.4 after the first year has also been considered a poor response [90]. The most important factor influencing the growth response during the first year is the severity of GHD [91,93]. Genetic and epigenetic factors can also be involved in rhGH responsiveness. Garner et al. [95] have recently reported that the pre-treatment transcriptome can predict first-year therapy response in GHD patients treated with daily rhGH or weekly long-acting GH (LAGH). These observations need further validation. In the last few years, studies have proposed some prediction models that can help clinicians in clinical practice by estimating patients’ response to treatment [96–99]. The burden of daily injection can cause adherence issues in children on GH therapy [100], and catch-up growth is reduced in patients with poor adherence [101].

GH therapy should be continued until the attainment of adult height (HV < 2 cm/year and/or full bone maturity). GH secretory capacity should be retested in selected individuals in order to confirm the diagnosis in adult life. If the diagnosis of GHD is confirmed, the patients may need to continue GH therapy during adulthood [102].

4.2. Long-Acting GH Formulations

A number of different technologies have been studied to prolong GH’s half-life. The first long-acting GH (LAGH) formulation was approved in 1999 [103], but due to injection-site reactions, it was withdrawn five years later. Recently, weekly LAGH formulations have been introduced that may overcome the burden of daily injections. LAGH formulations with weekly activity have been approved for GHD treatment in childhood by the FDA (Food and Drug Administration) and EMEA (European Agency for the Evaluation of Medicinal Products). Short-term studies have shown their efficacy and safety. LAGH formulations are not inferior to daily GH administration, and the safety profile is similar. [101,104,105]. Post-marketing surveillance in the coming years is essential to fully ascertain the benefits of LAGH over daily injections and the possible safety issues [106]. Currently, LAGH drugs approved for the use in GHD pediatric patients are somatrogen, somapacitan, lonapegsomatropin (approved in USA), Jintrolong (approved in China) and LBO3002 (approved in South Korea). The characteristics of these formulations are summarized in Table 2.

Table 2. Approved LAGH formulations.

Drug	Company	Technology	Frequency	Status
Somatrogen	OPKO Health Miami, USA and Pfizer New York, USA	GH fusion protein (carboxy-terminal peptide of hCG beta-subunit	Weekly	Initially approved in Australia in 2021 and subsequently in many countries (i.e., Europe, USA, Canada, Japan, Taiwan, Switzerland, United Arab Emirates, India, Brazil) Same efficacy and safety as daily hGH [101,107]
Somapacitan	Novo Nordisk, Bagsværd, Denmark	Albumin binding GH compound (single point mutation in GH with albumin binding moiety attached	Weekly	Initially approved in 2021 in Europe and subsequently in many countries (i.e., USA, South Korea, Canada, Japan, Brazil, Taiwan, Argentina, Saudi Arabia, Australia, India) Same efficacy and safety as daily hGH [108–110]
Lonapegsomatropin	Ascendis Pharma, Copenhagen, Denmark	Pro-drug (GH bound to a methoxy polyethylene glycol carrier via a self-cleaving linker)	weekly	Approved by FDA in 2021, available in USA Same efficacy and safety as daily hGH [101,111]

Table 2. Cont.

Drug	Company	Technology	Frequency	Status
Jintrolong	GeneScience Pharmaceuticals Co., Changchun, China	PEGylated formulation	Weekly	Approved in China since 2014 Same efficacy and safety as daily hGH [101,112]
Eutropin Plus	LG Life Sciences, Seoul, South Korea	Depot formulation (microparticles containing GH incorporated into sodium hyaluronate and dispersed in an oil base of medium-chain triglycerides	weekly	Approved in 2013; available only in South Korea Same efficacy and safety as daily hGH [101,113]

4.3. Safety

The safety of long-term GH therapy has been confirmed in many studies [11,12]. A number of potential adverse events are associated with rhGH therapy and need to be monitored. In the short term, the most common complaint in children treated with rhGH is headache, which is usually transient and benign. Intracranial hypertension with increased intraocular pressure (pseudotumor cerebri) and slipped capital femoral epiphysis have been also described. Benign intracranial hypertension should be suspected when patients complain of nausea, headache, dizziness and visual disturbance [114]. An ophthalmological referral with fundus oculi evaluation may be requested because, if adverse effects are confirmed, treatment with rhGH should be withdrawn and resumed at a lower dose [114]. Slipped capital femoral epiphysis must be suspected when patients complain of non-traumatic hip, thigh or knee pain, which may or may not be associated with limping and inability to bear weight. An orthopedic referral could be necessary in these cases. Childhood cancer survivors who were treated with total body irradiation are at higher risk for this adverse event [115]. Moreover, a progressive worsening of pre-existing scoliosis may become evident due to the rapid growth gain following rhGH therapy. Other side effects have been described in rare cases and include an increase in growth of non-malignant nevi, transient gynecomastia, carpal tunnel syndrome, musculoskeletal problems due to water and sodium retention with arthralgia and edema (more frequently reported in adults), tonsillar hypertrophy with exacerbation of obstructive sleep apnea and pancreatitis. The causal relationship of these adverse events with rhGH therapy is still controversial [116].

In the long term, insulin resistance and an increased risk of malignancy are the most feared adverse events. Development of disorders of glucose tolerance, insulin resistance and type 2 diabetes mellitus may occur in patients treated with rhGH, but the clinical significance appears to be low [117]. While rhGH decreases insulin sensitivity, GHD patients may have abnormalities in glucose metabolism due to impaired body composition, which can be corrected by rhGH treatment.

An increased risk of malignancy has been hypothesized to be caused by rhGH treatment in children, due to the observation that non-GHD adults with high IGF-1 levels present an increased risk of breast and prostate tumors [118]. However, an increase in the risk of new primary malignancies in GHD children and adolescents treated with rhGH has not been reported [12]. Conversely, there have been some reports of a small increase in secondary malignancies (bone, melanoma, brain, thyroid and leukemia) [29] in patients with GHD and a concurrent history of malignancy. Other studies do not confirm these results. In particular, no significant increase in new cases or in the relapse of previous leukemia has been found despite hundreds of thousands of patient-years of exposure [119]. Similarly, childhood cancer survivors treated with rhGH do not appear to have an increased risk of secondary malignancy except for benign meningiomas after radiotherapy of certain brain tumors [120]. However, there is still no consensus on the management of growth hormone therapy in patients with residual tumors and GHD [121].

Finally, the mortality rate in GHD subjects is difficult to assess, and this is due to the multiple possible associated comorbidities associated with GHD. A study reported by the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) group [122] did not confirm a clear association between rhGH therapy and mortality risk.

Subjects from eight European countries who have been treated with GH since 1984 have been collected to evaluate the prevalence of cancer and identify cause-specific mortality. The French report noted a 33% increase in all-cause mortality, with a higher prevalence in patients receiving a high rhGH dose ($>50 \mu\text{g/kg/day}$), while other reports from the Netherlands, Belgium and Sweden and the last updated SAGhE report [122] did not confirm these findings. Conversely, in patients with increased risk (i.e., comorbidities or MPHD), there was an increased hematological and cardiovascular mortality rate associated with the underlying conditions [122]. Both in the SAGhE study [122] and in other studies [123] mortality was not associated with the mean daily or cumulative rhGH dose. The data reported by the Kabi/Pfizer International Growth Database (KIGS), a large, international database of 83,803 children treated with rhGH, confirm that rhGH therapy is safe, with no reports of unexpected adverse events [89].

5. Conclusions

In conclusion, the diagnosis of IGHD can be straightforward or represent a clinical challenge. The use of GHSTs and the interpretation of the results are still discussed, but great advances have been made with the help of neuroimaging and genetics. Occasionally, IGHD may progress to MPHD, and, for this reason, these patients need long-term follow-up with regular evaluation of pituitary function. The use of LAGH preparations has been shown to be as effective as daily administration with less discomfort for the patient. Long term GH therapy has a good safety profile in all long-term studies.

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