Growth hormone and early treatment

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Growth hormone (GH) treatment is approved by the US Food and Drug Administration (FDA) not only for GH deficiency (GHD) but also for other childhood growth disorders with growth failure and/or short stature. GHD is the most frequent endocrine disorder presenting with short stature in childhood. During neonatal period, metabolic effects due to congenital GHD require a prompt replacement therapy to avoid possible life-threatening complications. In childhood and adolescence, growth impairment is the most evident effect of GHD and early treatment has the aim of restore normal growth and to reach normal adult height. We reassume in this review the conditions causing GHD and the diagnostic challenge to reach an early diagnosis, and an early treatment, necessary to obtain the best results. Finally, we summarize results obtained in clinical studies about pediatric patients with GHD treated at an early age, in which a marked early catch-up growth and a normalization of adult height were obtained

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G rowth hormone (GH) deficiency (GHD) is the most frequent endocrine disorder presenting with short stature in childhood and the most common pituitary hormone deficiency.

It can manifest differently according to the age of onset (early after birth, during childhood, at puberty or in adulthood), the cause or mechanism (genetic, idiopathic or acquired), intensity of deficiency and whether it is isolated or combined with that of other pituitary hormones or forms part of a complex syndrome.

Two different situations are possible in which early diagnosis and consequent early treatment are essential: the neonatal period (congenital GHD) and childhood or adolescence (congenital or acquired).

During neonatal period, metabolic effects due to congenital GHD are preminent and require a prompt replacement therapy to avoid possible life-threatening complications.

In childhood and adolescence, growth impairment is the most evident effect due to GH deficiency and early treatment has the aim of restore normal growth and to reach normal target height. If not treated, children with severe congenital GHD achieve (in historical populations) only 70% of their full growth potential. Children with less severe

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deficiency present later in life with variable short stature and reduced growth velocity. Its frequency is extimated around 1:3500-4000, but a milder phenotype has a higher frequency at about 1:2000.[1]

GH has other essential biochemical and metabolic actions other than promoting growth, and replacement treatment is needed to avoid possible complications due to its deficiency, both in children and in adults.[2] In children with multiple pituitary hormone deficiency (MPHD), replacement should also be directed at other hormonal deficiencies but these treatments (and GH in adults) will not be object of this review.

Recombinant human GH treatment is approved by the US Food and Drug Administration (FDA) not only for GHD but also for other childhood growth disorders with growth failure or short stature: Turner Syndrome (TS), chronic renal insufficiency (CRI), Prader-Willi Syndrome (PWS), small-for-gestational age (SGA) with failure to catch up to the normal height percentiles, short stature homeobox-containing (SHOX) gene haploinsufficiency (SHOXD), Noonan Syndrome (NS) and idiopathic short stature (ISS). However, these approved indications may vary in different countries.

We reassume in this review the conditions causing GHD and the diagnostic challenge to reach an early diagnosis, and consequently, an early treatment, necessary to obtain the best results. Finally, we summarize results obtained in clinical studies about pediatric patients treated at an early age with GHD.

GHD

Congenital hypopituitarism denotes underproduction of GH alone or in combination with deficiencies of other pituitary hormones present just in the neonatal period. It is a rare disease: the incidence is thought to be between 1 in 4000 and 1 in 10,000 live births. Diagnosis may be posed either in the neonatal period (clinical presentation ranging from absent to severe nonspecific symptoms) or in early to mid-childhood, more frequently for short stature.

Severe GHD of the newborn, most commonly isolated (IGHD) or as part of a multiple pituitary hormone deficiency (usually TSH and/or ACTH) (MPHD), can cause life-threatening hypoglycemias often beginning in the first few days of life, but also after the neonatal period.

Clinical presentation usually includes, besides of symptomatic hypoglycemia, which may result in a true neonatal emergency, with seizures, apnea and cyanosis, asymptomatic hypoglycaemia and prolonged jaundice (elevation of both conjugated and unconjugated bilirubin and often diagnosed as neonatal hepatitis), dysmorphic feature with midline defects, ocular and craniofacial anomalies, microphallus in males, often with undescended testes, and growth failure. Alternatively, they may be initially asymptomatic but at risk of developing pituitary hormone deficiencies over time. In fact, hypopituitary phenotypes can be highly variable and can evolve; diagnosis is often delayed and a careful and ongoing assessment is therefore critical in the evaluation of these patients, to prevent the morbidity and mortality associated to untreated hormonal abnormalities.[3]

Diagnosis

In each case of unexplained neonatal hypoglycemia, midline defects and short length at birth, a GH deficiency must be excluded. Reviews and consensus papers on the diagnosis of GHD repeatedly state the lack of a practical evidence-based approach to the diagnosis of GHD in the newborn. In the neonatal period it can be classically made on the basis of a GH level <20 ng/mL during hypoglycemia or after glucagon stimulation test, but, in the presence of clinical evidence, the diagnosis of severe neonatal GHD can be confirmed during the first week of life by a single randomly taken GH level less than 7 ng/mL, and also it can be performed in newborn screening cards.[4]

After the diagnosis of congenital GHD, multiple or isolated, a magnetic resonance

imaging (MRI) of hypothalamic-pituitary axis and a genetic analysis should be performed.

MRI

MRI is useful to investigate the etiology of GHD and the possible associated structural anomalies of the brain, hypothalamic-pituitary axis and the optic nerves. On the other hand, an endocrine evaluation and neuroimaging of the CNS including the pituitary region should be considered also in patients with ophthalmological symptoms [5].

Patients with congenital hypopituitarism might have the classic triad of pituitary stalk interruption syndrome: an interrupted or thin pituitary stalk, an absent or ectopic posterior pituitary (bright spot on MRI) (EPP), and anterior pituitary hypoplasia or aplasia. Associated abnormalities may include optic nerve hypoplasia (and other ophthalmological anomalies), absent septum pellucidum (or agenesis of the corpus callosum), septo optic dysplasia (SOD) and Arnold-Chiari I malformation.

Patients with hypothalamic-pituitary structural abnormalities (triad of pituitary stalk interruption syndrome and expecially patients with SOD), have more frequently severe phenotypes and additional hormonal deficiencies (TSH>ACTH>LH/FSH>ADH) other than GHD. On the other hand, children with MPHD were more likely to have structural anomalies on MRI and the classic triad is the most common finding (90%).[6] MRI pattern is important for treatment and follow-up: after a mean follow up period of 4.5 years, 5.4% of subjects with IGHD and abnormal MRI progressed to MPHD while none of those with normal MRI progressed.[7] The sex ratio is approximately equal for patients with SOD, but there was a significantly higher proportion of males (approximately 70%) in the EPP, pituitary hypoplasia, stalk defects, and triad categories.[8] MRI abnormalities correlate best with severity of GH deficiency rather than number of hormone deficiencies and breech presentation.[9]

Genetics

Most cases of congenital GHD are sporadic, but genetic background is frequently present.[10] With expanding knowledge of the genes that direct pituitary development or hormone production, an increasing proportion of cases can be attributed to a specific genetic defect. Mutations in 7 candidate genes account for 13% of IGHD and 20% MPHD cases. The likelihood of finding mutations is increased by positive family histories and by association with a significant malformation of the pituitary gland.[11] In these cases, genetic analysis may be considered and clinical, biological, and radiological work-up is important to determine for which transcription factor the patient should be screened. In fact, the embryonic development of the hypothalamo-pituitary axis is dependent upon the carefully orchestrated spatial and temporal pattern of expression between a number of signaling molecules and transcription factors. Genetic mutations in any of these factors necessary for pituitary embryogenesis and hormone secretion can lead highly variable phenotype [12]. Mutations in early developmental genes (e.g. HESX1, SOX2 and LHX3) are associated with complex pituitary phenotypes in association with a wide spectrum of craniofacial/midline defects ranging from incompatibility with life to holoprosencephaly (HPE) and cleft palate and SOD. Mutations in pituitary-specific genes such as POU1F1 and PROP1 are associated with pituitary-specific phenotypes and deficiency in one or more pituitary hormones.

The commonest genes implicated in genetic etiology of IGHD are those encoding growth hormone (GH1) and the receptor for GH-releasing hormone (GHRHR). Rarely, it is caused by mutations in transcription factors (as seen above) or be the first presentation before the development of other pituitary hormone deficiencies.[13]

Genetic studies of affected patients and their families provide insights into possible mechanisms of abnormal pituitary development and GH secretion or action; however, the overall incidence of mutations in

known transcription factors in patients with MPHD or IGHD is relatively low, indicating that many genes remain to be identified.[14]

Genetic diagnosis is useful also for follow-up. In fact, the clinical presentation of pituitary hormone disease may be dynamic as subsequent additional hormone deficiencies may develop over time (for example, late-onset corticotroph deficiency in patients with PROP1 mutations) and lifelong follow-up of these patients is, therefore, recommended.[15] Characterization of patients with genetic mutations allows early treatment of pituitary deficiency with an appropriate replacement of hormone deficiencies and decrease the morbidity and mortality in patients with IGHD [16] or MPHD.[17] Thus, genotyping appears highly beneficial for the early treatment of the patient but also for the family.[18] In fact, depending on the type of transmission (recessive transmission for PROP1 and LHX3, dominant for LHX4, autosomal dominant or recessive for POU1F1 and HESX1), genetic counseling might be proposed.

Anyway, the majority of patients presenting with short stature do not receive a definitive diagnosis. Advances in genetic sequencing using next-generation DNA sequencing technology allow for large-scale screening of candidate genes, potentially leading to rapidly identify genetic etiologies of short stature, but data interpretation is still complex.[19]

These advances in genetic background of short stature and in pharmacogenomics will also optimize the treatment of growth hormone deficiency and other conditions associated with short stature, for which recombinant human growth hormone is a licensed therapy.[20]

Growth in congenital GHD

The child with congenital hypopituitarism is usually of normal (or moderately reduced) size and weight at birth, although those with MPHD and genetic defects have birth lengths that average 1 SD below the mean. Subsequently, there is a rapid growth impairment and reduction in height SDS in the first months of life.[21] Children with untreated severe defects in GH production or action are often more than 4 SD below the mean by 1 yr of age and achieve only 70% of their full growth potential, leading to a deficit on average of 38 cm in males and 33 cm in females. Children with less severe deficiency present later in life with reduced growth velocity (below the 25th percentile for age) and gradually diverge from normal height percentiles presenting short stature.

GHD in childhood and adolescence (idiopathic and acquired)

The principal mode of presentation of growth hormone deficiency after the neonatal period is with short stature and low growth velocity for age.[22]

Normal growth is a sign of good health and it is the result of a complex interaction between genetic, hormonal and environmental/nutritional factors. Assessment of a child's height and weight is one of the best indicators of his or her general health and well-being. On the contrary, abnormal growth might indicate the existence of underlying disease in an apparently normal child. Early detection and diagnosis of the causes of short stature allows management and minimizes the impact of any underlying medical condition, optimizing attainment of good health and normal adult height.[23] However, short stature in children is frequently unrecognized in early childhood and thus diagnosed later, which decreases the opportunity to intervene and improve both their health outcomes and stature.[24]

Early detection of growth disorders

Any assessment of height needs to be normalized relative to the population that the individual is from and an appropriate growth chart is an essential tool for the screening, surveillance and monitoring of children's growth. A diagnosis of short stature is usually based on a child's

height measurement lying below -2 SD on a growth chart.

As stature is influenced significantly by genetic factors, adult height can be predicted on the basis of adjusted midparental height (target height) that is the potential height of a child. Even if the actual height measurement is not below -2 SD and there is not short stature, a child whose height SDS falls outside the parental target range is more likely to have a growth disorder.

A normal child tends to follow a given centile line or pattern and the evaluation of growth velocity provides the earliest identification of problems with growth. Growth velocity is best assessed using measurements taken at 3- to 4-monthly intervals in infants and at 6-monthly intervals in older children. When growth slows and crosses the height SD lines or percentiles (growth retardation), even if still within the normal range on the growth chart, a pathological etiology is more likely.

Thus, a child may be of short stature in comparison to appropriate growth charts or respect to target height, or may have a reduced growth velocity for age and sex. In each of these three conditions a pathologic condition have to be early excluded or affirmed.

For a good differential diagnosis, a thorough medical and family history should complement the physical examination to determine signs, symptoms and clues that may indicate a specific disease, and analysis of the growth curve and weight-for-height measurements.

About a half of children or adolescents referred for short stature have normal variants and no underlying pathology causing their reduced height: many of these children may have constitutional delay in growth and puberty or familial short stature.

If these normal variants of growth are considered unlikely, it is important to investigate further to identify and treat a potentially serious condition initially manifesting as delayed growth.

The further below -2.0 SD an individual's growth falls, the more likely it is that the child is not growing normally and that there is a pathological condition potentially keeping him or her from achieving their genetically determined height potential.[25]

In a school-based study, 14% of children who were shorter than the 3rd percentile and growing at <5 cm/year had an underlying medical condition. For 5% of children the short stature was endocrine in origin.[26]

There are a number of conditions that might lead to a reduced growth rate and/or short stature,[27] which potentially could be detected early through growth monitoring. In particular, before all, chronic diseases and dysymorphic syndromes must be excluded.

Indeed, almost all chronic systemic diseases can cause growth impairment (often with decreased weight-for-height ratio), delayed puberty and bone age, to a degree that is dependent on the severity and treatment of the underlying disease. In some cases, only growth may be impaired for several years before other symptoms become evident.

On the contrary, a deceleration of linear growth in a well-nourished or obese child may be an indication of an endocrine cause of short stature such as GHD, hypothyroidism or glucocorticoid excess.

Genetic or syndromic causes of short stature are often diagnosed because of abnormalities found during clinical examinations. Disproportionate shortening of the limbs may suggest achondroplasia, whereas dysmorphic features of the eyes, ears or facial abnormalities may prompt chromosomal disorders such as Turner, Down or Noonan syndrome. Some girls with Turner syndrome may, however, have an entirely normal physical appearance, rather than the typical phenotype and, for this reason, a karyotype should always be considered in a short girl.

A change in the rate of growth during early childhood must always be investigated. In some children, growth may be normal until the age of 10-12 years, after which the rate of growth is markedly slowed. Constitutional delay of growth and puberty may be the cause of this growth deceleration and it will be followed by a spontaneous

acceleration of growth associated with the pubertal growth spurt. Unfortunately, this same pattern of growth deceleration can be associated with a pathologic growth delay and careful investigation is thus always required.

Moreover, with the increasing numbers of survivors of cancer therapy, it has become important to identify and treat short stature presenting in such cases.

The most useful test in distinguishing the short normal child from one with a pathologic condition is accurate growth assessment, by measuring children height early and often, with calculation of growth velocity. Children who are short but growing at a normal growth velocity are most probably healthy; in contrast, a child whose growth velocity is declining, irrespective of their absolute height, must be carefully evaluated.

Prompt recognition of the cause of abnormal growth, provides the best chance for a child to achieve a good health outcome as well as the potential to reach a normal adult height. This is particularly important in case of remediable endocrinological or non-endocrinological pathologies, in which the clinical significance of early recognition of short stature is clear.

The child with short stature or growing below the normal range must be referred to a specialist. In fact, the possibility for proper treatment depends both on the early identification of these children and on appropriate evaluation by knowledgeable clinicians.

In an evidence-based guideline for the referral of children with short stature,[28] a low height SDS (height SDS<3 percentile) was shown to be the most useful criteria for detecting short stature in children <3 years of age. In older children (3-10 years), combined use of 'short for target height' (height SDS minus target height SDS<2) and height SDS<2.5 as well as height deflection (height SDS decrease >1.0 SD) provided the best means of identifying children with short stature.

Amongst the 2775 children referred for specialist follow-up for short stature in Germany,[29] there were 38 new cases of GHD (1:1605 children screened), four new cas-

es of Turner syndrome (1:15 246 children screened), two new cases of juvenile hypothyroidism (1:30 492 children screened) and three new cases of psychosocial growth failure (1:20 328 children). Endocrine disorders are rarely the cause of short stature, but when present are highly treatable, so are especially important to diagnose early.[23]

Even if growth monitoring is performed, children with treatable causes of abnormal growth are frequently referred late to a specialist unit,[30] received a diagnosis and treatment at an older than optimal age, precluding the opportunity for the child to achieve normal or near normal height.[31]

Clinical appearance of GHD

The phenotypic features of GHD include characteristically immature facies with a prominent forehead and depressed midline development. The head is round, the face is short and broad, and the bridge of the nose is depressed and saddle-shaped. The nose is small, and the nasolabial folds are well developed. The eyes are somewhat bulging. Associated abnormalities include midline defects of the face, a single central incisor, or optic nerve hypoplasia. Bone maturation and dentition are delayed. The mandible and the chin are underdeveloped. The neck is short, the larynx is small and the voice is high-pitched and remains high after puberty. The hair may be thin and sparse, nail growth slow.

The extremities are well proportioned, with small hands and feet. Length is mainly affected, weight for height is usually normal, but body composition is characterized by an excess of subcutaneous fat and a deficiency of muscle mass that contributes to a pudgy appearance. The genitals are usually small for age, and sexual maturation may be delayed or absent. Facial, axillary, and pubic hair usually is lacking, and the scalp hair is fine. Symptomatic hypoglycemia, usually after fasting, occurs in 10-15% of children with panhypopituitarism and those with IGHD. Intelligence is usually normal.

Acquired hypopituitarism

Acquired hypopituitarism usually has a later onset and different causes than congenital hypopituitarism. Acquired GHD is idiopathic in the majority of diagnoses, but any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary can cause pituitary hormone deficiency. In fact, it may result from tumors (craniopharngioma, glioma), histiocytosis, traumatic head injury, CNS infection or irradiation, or surgical damage to the pituitary or hypothalamus.

Because such lesions are not selective, multiple hormonal deficiencies are usually observed but the GH axis is the most susceptible to disruption by acquired conditions.

The child is initially normal, and manifestations similar to those seen in idiopathic pituitary growth failure gradually appear and progress, together with signs and symptoms related to deficiency of other endocrine functions under pituitary control. Moreover, if the lesion is an expanding tumor, symptoms such as headache, vomiting, visual disturbances, pathologic sleep patterns, decreased school performance, seizures, polyuria can occur. Visual field defects, optic atrophy, papilledema, and cranial nerve palsy are common in children with craniopharyngiomas. Slowing of growth can antedate neurologic signs and symptoms, especially with craniopharyngiomas, but symptoms of hormonal deficit account for only 10-20% of presenting complaints.

A retrospective, single-center, cohort study of 176 patients (93 boys), aged 6 years (range, 0.2-18 years), with hypothalamic-pituitary lesions was performed to investigate clinical and endocrine presenting symptoms to determine if diagnosis of hypothalamic-pituitary lesions in children could have been made more rapidly if an earlier referral had been made.

The most common presenting symptoms were neurologic (50%) and/or visual complaints (38%), followed by solitary endocrine symptoms (28%). For 122 patients with neuro-ophthalmic presenting symptoms, the mean symptom interval was 0.5 year, although 66% of patients had abnormal Body Mass Index (BMI) or growth velocity, which preceded the presenting symptom interval onset by 1.9 years and 1.4 years, respectively. Among them, 41 patients were obese before diagnosis and 35 of them had normal growth velocity at the onset of obesity. Thus, endocrine disorders occurred in two-thirds of patients prior to the onset of the neuro-ophthalmic presenting symptom but were missed [32]. Earlier identification of endocrine disorders by appropriate plots of height, weight, and BMI may help shorten the time for diagnosis of hypothalamic-pituitary lesions, as a change in these measurements preceded the onset of neuro-ophthalmic presenting symptoms in a substantial number of cases by several years.[33]

Early diagnosis of GHD

GH deficiency is suspected in children with moderate to severe postnatal growth failure: height below -2 SD for age and sex or height >2 SD below sex-adjusted mid-parental height. Acquired GH deficiency can occur at any age, and when it is of acute onset, height may be within the normal range. A strong clinical suspicion is important in establishing the diagnosis because laboratory measures of GH sufficiency lack specificity.

Observation of low serum levels of IGF-1 and the GH-dependent IGF-BP3 can be helpful, but they should be matched to normal values for skeletal age rather than chronological age and there is an overlap between levels in normally growing children and those with hypopituitarism. Values in the upper part of the normal range for age effectively may exclude GH deficiency.

Diagnosis of GH deficiency traditionally requires demonstration of absent or low levels of GH in response to stimulation with provocative tests. These include administration of insulin, arginine, clonidine, glucagon and others. In chronic GHD, the demonstration of poor linear growth, delayed skeletal

age, and low peak levels of GH (<10 ng/mL) in two provocative tests are compatible with GH deficiency. In acute GH deficiency, a high clinical suspicion of GH deficiency and low peak levels of GH (<10 ng/mL) in two provocative tests are compatible with GH deficiency. In addition to establishing the diagnosis of GH deficiency, it is necessary to examine other pituitary functions and search for the etiology of the disease by MRI.

There is a wide range of spontaneous GH secretion in normally growing prepubertal children and considerable overlap with the values observed in children with classic GHD. Thus, although the clinical and laboratory criteria for GH deficiency in patients with severe (classic) hypopituitarism are well established, the diagnostic criteria are not well settled for short children with lesser degrees of GHD.

The diagnosis of GHD in childhood is guided by recommendations of national and international consensus statements which are based on the experience of experts: most of these recommendations reach only a low level of evidence.[34]

Cut-offs for GH response to stimulation tests were central part of these recommendations, and their definition however was arbitrary. Some authors suggest the substitution of arbitrarily defined GH cut-offs by those based on auxology. They obtained the best diagnostic accuracy at a peak GH cut-off for arginine of 6.6 µg/L and at a peak GH cut-off during spontaneous secretion at night of 7.3 µg/L, lower than standard cut-off levels. Importantly, children diagnosed as GHD in the past with GH test values above the new cut-offs showed a lower response to GH.[35]

Moreover, GH stimulation tests are still subject to debate. For example, BMI affects peak stimulated GH and a higher BMI SDS, even within the normal range, may lead to overdiagnosis of GH deficiency.[36] To achieve greater diagnostic specificity, some researchers suggest that 3 days of estrogen priming should be used before GH testing, while others consider priming only in adolescents with pubertal delay (girls >11.5-12 years and boys >13-13.5 years exhibiting no evidence or only initial signs of puberty).[37]

Diagnostic strategies for distinguishing between permanent GHD and other causes of impaired growth are imperfect. Children with a combination of genetic short stature and constitutional delay of growth have short stature, below-average growth rates, and delayed bone ages. Many of these children exhibit minimal GH secretory responses to provocative stimuli and are diagnosed as GHD and treated with hGH, but when they are retested as adults, the majority have peak GH levels within the normal range.

The clinical and biochemical diagnoses continue to be a conundrum despite efforts to harmonize biochemical assays for GH and IGF-1 analysis, probably also because the diagnosis based on the so-called GH secretion stimulation tests will prove to be of limited usefulness for predicting therapy indications.[38, 39] Because of this intrinsic diagnostic inaccuracy of any GH test, the correct selection of the child to be tested remains of utmost importance.

Treatment with hGH

The objectives of GH treatment in GHD are to improve metabolic disturbances in the neonate and to correct poor growth and short stature in children, to obtain a final height within normal limits with respect to the genetic potential.

In neonates with congenital GHD and persistent hypoglycemia, GH replacement may be needed just in the neonatal period. As growth failure may be early and severe in these patients, GH treatment should be considered early also in cases without hypoglycaemia. Delivery devices are designed for larger children, and usually the lowest practical dose is 0.2 mg/day subcutaneously.

In children with classic GH deficiency, treatment should be started as soon as possible to correct the growth deficit narrowing the gap in height between patients and their classmates during childhood and to have the greatest effect on mature height.

For pediatric patients, guidelines for the use of GH have been developed by several organizations [40] and periodically updated [41, 42] that have identified specific criteria for initiating GH therapy for each FDA-approved indication.

The recommended dose of GH in GHD is 22-50 μg/kg/day during childhood, administered subcutaneously. Therapy should be continued until near-final height is achieved or a bone age >14 years in girls and >16 years in boys is reached.

Some patients develop either primary or central hypothyroidism while under treatment with GH. Similarly, there is a risk of developing adrenal insufficiency, that, if unrecognized, can be fatal. Periodic evaluation of thyroid and adrenal function is therefore indicated for all patients treated with GH.

Maximal response to GH occurs in the 1st yr of treatment and then the growth rate tends to decrease. Growth response is variable, and an accepted definition of poor/good response is lacking. Significant predictive factors of good response are: height velocity at 4 months, and baseline BMI SDS (positively correlated), baseline age, baseline height SDS, and baseline IGF-I SDS (negatively correlated). Thus, although some pretreatment characteristics and early growth response may guide GH therapy,[43] there are no methods that can reliably predict which of these children will become taller in adulthood as a result of GH treatment or will have compromised adult height, and few experts use prediction models in clinical practice.[44]

Successful therapy results in the patient attaining mid-parental height, and relies on correct diagnosis and early treatment initiation to optimize growth outcomes.

Long-term results of this treatment and final height gain depend from several factors, including target height, height and bone age deficit at the start of treatment, doses of GH, duration of treatment, and frequency of growth hormone injections, height at the start of puberty and age at the onset of treatment, earlier treatment resulting in higher adult heights. Interestingly, because age at onset of treatment is inversely correlated with the growth response, and smaller lighter children require lower doses of GH, initiating treatment at an early age has also associated economic benefits.[45]

The first-year increase in height SDS and prepubertal height gain was highly correlated with total height gain, confirming the importance of treatment before pubertal onset.[46]

It is possible to achieve FH within the midparental height range in patients with idiopathic GHD treated from an early age with GH, but absolute height outcomes remain often in the lower part of the normal range. Thus, delays in both diagnosis and initiation of therapy continue to compromise adult height.[47]

Poor growth may be in some part due to low adherence to GH therapy regimens; indeed up to 50% of children are less than fully compliant with treatment. The effort to make the administration of GH easier and less painful for the patient, will probably improve treatment adherence and outcome benefits.[48]

On the other hand, individual sensitivity to recombinant hGH is variable. Identification of specific growth-related genetic markers associated with growth response (pharmacogenetics) could have a role for individualization of management, improving prediction, enabling early therapy modulation and individualization of the GH dose [49] and duration of treatment to obtain better results.[50]

Results of early GH treatment in GHD

GHD in children is very heterogeneous in terms of its etiology, pathogenesis, and the age at which it is diagnosed. Even among children with evidence of congenital GHD, it is not unusual for the diagnosis to be established during a relatively late stage of childhood, at a time when short stature becomes obvious.

There is, however, a subset of patients whose GHD is recognized during infancy or early childhood (i.e. <3 years), and reports in short-term and long term studies have

shown a marked early catch-up growth and a normalization of height with the initiation of treatment in infancy and early childhood. The main results of these studies are shown in Table I and are reported here in chronological order.

In 1995 Boersma *et al.* studied catch-up growth of 26 children with GHD during four years of GH treatment, which was started before 3 years of age. Mean height SD score increased from -4.3 to -1.9. Height SD score after four years correlated positively with injection frequency and height SD score at start of treatment. In patients

with an initial height SD score between -2 and -4, catch-up was remarkable, while children with an initial height SD score <-4 did not reach full catch-up growth within four years. The authors concluded that early treatment of GHD children leads to an adequate catch-up growth over four years if the initial height SD score is not less than -4. This emphasizes the importance of early diagnosis and treatment, before the statural impairment become particularly evident.[51]

Always in 1995 Arrigo *et al.* studied retrospectively 23 children with early onset (congenital) GHD treated before 5 years

TABLE I.—*Effects of treatment with GH beginning in infancy and childhood.*

Study	year	n	Age at start (yrs)	Initial Height SDS	Duration (yrs)	Final Height SDS	Results	Comments
Boersma [51]	1995	26	<3	-4.3	>4	-1.9	Adequate catch up growth	Importance of early diagnosis and treatment
Arrigo [52]	1995	23	<5	-4.0	>8	-1.5	Predicted ultimate height significantly greater than the pretreatment height and not different from the target height	Treatment has to start during the first years of life and GH doses have to be adjusted periodically for weight changes
Rappaport [54]	1997	25	<3	-3.6	>5	-0.8	GH deficiency should be treated as soon as diagnosed	Growth at a rate normal for age in patients diagnosed before growth retardation
Wasniewska [56]	2000	12	<2	-3.7	>7	-0.7	Average height not significantly far from mean TH and average PH very close to TH	Importance of early diagnosis and treatment of GHD; both catch-up growth under therapy and PH are positively influenced by birth weight
Ranke [59]	2005	265	<3	-3.1	>1	-1.5	Early replacement of GH in younger children with GHD is more effective in achieving height improvement than when the treatment starts later in childhood	Early detection and GH treatment of congenital GHD is advantageous as a cost-effective strategy for achieving greater improvement of absolute height and growth velocity
Root [60]	2011	47	<2	-2.3	>11	-0.4	mean NAH was comparable to the target height	Normal pattern of linear growth during childhood and adolescence and satisfactory NAHs can be achieved in the majority of patients when treatment of the GHD subject is begun during infancy
Huet [58]	2012	49	<1	-3.5	16 (+/-1.6)	-0.1*	mean gap between final size and parental target size of only 0.1 +/- 1.1 SD	Early diagnosis and treatment are essential

FH: final height; CA: Chronological age, PH: predicted height; NAH: near adult height; TH target height * respect to target height

of age (range 0.4-4.9 years) with GH at the dose of 0.1 U/kg/day (adjusted for weight every 3 months) for 8 years. As a consequence of the significant growth acceleration induced by GH treatment, the patients' height deficiency at the last check was significantly less severe than before treatment and the predicted ultimate height, significantly greater than the pretreatment height, did not differ from the target height. The conclusion was that catch-up growth to the target percentile in GHD patients is possible, provided that substitutive treatment is begun during the first years of life and that GH doses are adjusted periodically.[52]

In an subsequent experience of the same multicentric group (De Luca *et al.* 1996), 13 patients were treated from 5 years until adulthood. They attained an adult mean height that did not differ from the midparental height (-0.9 *vs.* -0.7 SDS). In eight subjects final height exceeded the respective target height and only three patients failed to achieve an end height within the target range. Height outcome correlated negatively with chronological age at therapy initiation and positively with height at puberty onset.[53]

In a non-comparative multicenter prospective study (Rappaport *et al.* 1997), 49 children with isolated GH deficiency (N.=19) or multiple pituitary hormone deficiency (N.=30) treated before the age of 3 yr with daily s.c. injections (0.6 U/kg.week) for 3-5 yr were studied. Patients were divided into two groups according to their height SD score for chronological age at the initiation of therapy: group A consisted of 8 patients presenting an initial height within the normal range (<2 SD below the mean), and group B consisted of 25 children with initial growth retardation (>2 SD below the mean). In group A, the mean height SD score increased from -1.1±0.6 to 0.35±1.0 SD in the first year and remained in the normal range throughout the following 4 years. In group B after 5 years of treatment, the mean height SD score for age had increased from -3.6±1.0 SD to -0.8±1.2 SD, with an incomplete catch-up growth, and four patients (16%) remained below -2SD for CA. The 5-yr height gain was negatively corre-

lated with the height SD score at the start of treatment and the first year height gain was the most predictive parameter. There was no significant influence of other factors, such as intrauterine growth retardation, body mass index and age at the start of treatment, or parental target height. The rapid and almost complete return to normal growth and height for age obtained in this study supports the need for GH treatment early in GH-deficient children, as soon as diagnosed, before growth retardation become evident.[54] This is particularly of importance in congenital GHD diagnosed in the neonatal period.

Similar results and conclusions were reported in studies first by Arrigo *et al.* in 1998 and then by Wasniewska et al. in 2000 regarding patients treated before 2 years of age. They stated the importance of both early diagnosis and long-lasting treatment[55] for attaining an average height not significantly far from mean target height. They showed also that both catch-up growth under therapy and predicted height at the end of the 7-year treatment period were positively influenced by birth weight (BW).[56]

In some studies by French multicentric experience[57] in 49 patients that started GH treatment before 1 year of age (Huet *et al.* 1999), mean height reached -0.4 SDS after a mean duration of GH therapy of 8.0±3.6 years; change in height SDS was +3.11±2.06 SD, exceeding 4 SDS in 19 patients. Catch-up growth was maximal during the first 3 years. At 10 years of age the patients had reached or even exceeded their target size. During puberty an acceptable growth spurt but no further catch-up growth was reported. After growth hormone for an average of 16±1.6 years. Final height was 159±8 cm in girls and 173±7 cm in boys. No adverse effects of growth hormone therapy were reported. Thanks to early GH treatment, children with hypopituitarism had a mean gap between final size and parental target size of only 0.1±1.1 SD. Early diagnosis and treatment are therefore essential in this setting.[58]

Also in these studies growth retardation at diagnosis was inversely correlated with total catch-up growth. However, no correla-

tion between first year catch-up growth and further changes in height SDS was found, underlining the difficulty in identifying "responders" to GH treatment on the basis of the first year's result.

In children, GH secretion and sensitivity to GH are influenced by developmental changes.

In a study from Ranke *et al.* a cohort of 265 children with idiopathic GHD, with treatment started at less than 3 years of age was compared with a cohort of 509 children with treatment started at 7-8 years of age to clarify whether the response to GH in very young children with GHD is the same as that in older, prepubertal children. After the first year of GH, there was a greater gain in height per GH dose unit in the very young than in the older children. The early detection and GH treatment of congenital GHD is advantageous as a cost-effective strategy and is more effective for achieving greater improvement of absolute height and growth velocity than when the treatment starts later in childhood.[59]

Forty-seven patients with GHD in whom administration of GH was initiated at or before 2 years of age and who had achieved near-adult heights (NAH) were studied by Root et al.. After beginning treatment at a mean age of 0.9 years and height of -2.3 SD, these subjects achieved mean statures of -0.6, -0.3, and -0.4 SD at 5 and 10 years of age and at NAH, respectively, with a mean NAH comparable to the target height. Importantly, the interval of substantial growth retardation characteristic of the growth pattern of GHD subjects identified during childhood was avoided by initiation of therapy during infancy. Catch-up growth was achieved during childhood (before 10 years of age) and that no additional gain in NAH SDS was realized during puberty, consistent with the concepts that sensitivity to GH is greatest during childhood and that therapeutic efforts to maximize height should be concentrated in the prepubertal years. Tallest NAHs were realized by patients with uncomplicated courses whose heights were normal or tall when spontaneous puberty occurred or was induced.

Patients with severe prenatal or perinatal, congenital and acquired neurologic insults, precocious puberty, or associated illnesses achieved less optimal NAHs despite administration of rhGH. The authors concluded that a normal pattern of linear growth during childhood and adolescence and satisfactory NAH, appropriate for TH, can be achieved in the majority of patients when treatment of the GHD subject is begun during infancy.[60]

In conclusion, the long-term results now available show a favourable auxological outcome, compared with target height or historical height data from patients with severe hypopituitarism.

There are other aspects, such as assessments of the psychological and neurodevelopmental outcomes, that are necessary in order to evaluate in a complete way the "final results" of endocrine replacement therapies.[61]

Regarding neurodevelopmental aspects, children with isolated GHD have, compared with controls, white matter abnormalities in the corpus callosum and corticospinal tract and reduced thalamic and globus pallidum volumes that relate to deficits in cognitive function and motor performance. Follow-up studies that investigate the course of the structural and cognitive deficits on growth hormone treatment are now required to confirm that GHD impacts significantly on brain structure, cognitive function and motor performance [62]. These last results may be a further reason to diagnose and treat GH deficiency early with the aim to improve also neurocognitive and motor performances.

Remarkable points

— The majority of infants with idiopathic or organic GHD who began treatment with rhGH before 2 years of age experienced normal growth patterns during childhood and achieved NAHs within the normal range and appropriate for their THs.

— The interval of substantial growth retardation characteristic of the growth pat-

tern of GHD subjects identified during childhood was avoided by initiation of therapy during infancy; there is a need for GH treatment early in GH-deficient children, as soon as diagnosed, before growth retardation become evident

— Early detection and GH treatment of congenital GHD is advantageous as a cost-effective strategy and is more effective for achieving greater improvement of growth velocity and adult height

— Patients with uncomplicated courses whose heights were normal or tall when spontaneous puberty occurred or was induced have tallest NAH.

— Patients with severe prenatal or perinatal, congenital and acquired neurologic insults, precocious puberty, or associated illnesses achieved less optimal NAH.

— Assessments of the psychological and neurodevelopmental outcomes are necessary to evaluate the final results

Conclusions

Short stature should be identified, diagnosed and treated appropriately and without delay.

The most useful tests in distinguishing the short normal child from one with a pathologic condition are accurate height measurements over time and calculation of the growth velocity. Monitoring growth allows early detection of the causes of poor growth and early intervention optimizing the possibility of achieving good health and a normal adult height. This is particularly evident for GHD but also in other conditions in which GH is an approved indication. The early detection and GH treatment is advantageous as a cost-effective strategy and is one of the best factors for achieving a normal growth pattern during childhood and adult height within the normal range and appropriate for target height. Delayed referral for GH treatment is still frequent, therefore a guidance on optimal management of GH therapy is required, with focus on early diagnosis, dosing, treatment monitoring, adherence, and motivation.

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