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Review

Growth Hormone Deficiency

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Abstract: Short stature is a common reason for a child to visit the endocrinologist, and can be a variant of normal or secondary to an underlying pathologic cause. Pathologic causes include growth hormone deficiency (GHD), which can be congenital or acquired later. GHD can be isolated or can occur with other pituitary hormone deficiencies. The diagnosis of GHD requires thorough clinical, biochemical, and radiographic investigations. Genetic testing may also be helpful in some patients. Treatment with recombinant human growth hormone (rhGH) should be initiated as soon as the diagnosis is made and patients should be monitored closely to evaluate response to treatment and for potential adverse effects.

Keywords: growth hormone; short stature; hypopituitarism

1. Introduction

Short stature is defined as a height less than two standard deviations (SD) below the mean for age and sex. This corresponds to a height below the 2.3rd percentile. Height distribution follows a normal Gaussian distribution, and therefore, 2.3% of a population will meet this cutoff [1]. The majority of these individuals have a normal variant of short stature, while approximately 20% have a pathological cause including growth hormone deficiency (GHD), the focus of this review paper [2].

Normal variants of short stature include familial short stature (FSS), constitutional delay of growth and puberty (CDGP), and idiopathic short stature (ISS). FSS is characterized by a low-normal height velocity, a bone age that is consistent with the chronological age, and a final adult height that is short, however in line with the individual's genetic potential based on the parental heights [3]. It is important to note that a short child who has a short parent may have an underlying genetic cause that requires further evaluation. CDGP is evident in up to 15% of children and is seen twice as frequently in boys than in girls [4]. Individuals with CDGP typically have a normal length and weight at birth, however during the first few years of life, there is a deceleration in linear growth resulting in a downward crossing of height percentiles on the growth curve. This is followed by a normal growth rate during childhood and delay in the onset of puberty, which results in a marked discrepancy in height during the early adolescent years in comparison to age-matched peers. CDGP is characterized by delayed skeletal maturation, and this longer period of growth enables children to ultimately reach their target adult heights [5]. ISS is diagnosed when the individual's height is less than two standard deviations below the mean, however there is no identifiable cause or underlying disorder. It is made as a diagnosis of exclusion after other non-pathologic and pathologic causes have been ruled out [1].

Pathologic causes of short stature include disorders with secondary effects on growth (undernutrition, gastrointestinal disorders [Crohn's disease, celiac disease], cystic fibrosis, immune deficiencies with recurrent infections, renal disorders [chronic kidney disease (CKD), renal tubular acidosis (RTA)], systemic juvenile idiopathic arthritis (JIA), cancer and related treatments), endocrine disorders (GHD, hypothyroidism, Cushing syndrome, pseudohypoparathyroidism type 1), genetic diseases [Turner syndrome, Noonan syndrome, Silver-Russell syndrome], skeletal dysplasias, as well as glucocorticoid therapy [6–8].

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Growth hormone (GH) is released from somatotrophs in the anterior pituitary gland in a pulsatile manner due to opposing actions of growth hormone releasing hormone (GHRH) which has a stimulatory effect, and somatostatin (also known as somatotropin release-inhibiting factor or SRIF) which has a inhibitory effect [9]. There are numerous factors that affect GH section. Hypothyroidism as well as adiposity are associated with a decrease in GH secretion, while undernutrition leads to over secretion of GH (however with low levels of insulin-like growth factor-1 (IGF-1) levels indicating GH resistance) [9,10]. The majority of GH is found in the 22-kDa form (75%), however, smaller amounts of 20-kDa (5–10%) and 17.5-kDa (1–5%) peptides are also present [11]. Once released into circulation, GH stimulates fat breakdown and promotes protein synthesis [9]. Although GH can exert its effect directly at the cellular level, it primarily acts on the liver to synthesize IGF-1 which exerts peripheral growth promoting effects. IGF-1 circulates bound to IGF-binding proteins (IGFBPs), which extend the serum half-life of IGFs. IGFBP-3 is the major IGFBP in humans and transports the majority of circulating IGF-1 [12].

GHD can be either congenital, affecting approximately 1:4000–1:10,000 live births or acquired later in life, and can be isolated or associated with other pituitary hormone deficiencies. Although most cases of GHD occur sporadically, a first degree relative with this condition is identified in 3–30% of cases [11].

2. Molecular Genetics

GH is a peptide encoded by the GH1 gene, which is part of a 65-kb cluster of five genes located on chromosome 17q22-24 [11,13]. Four forms of familial isolated growth hormone deficiency (IGHD) have been described: autosomal recessive (type IA and IB), autosomal dominant (type II) and X-linked recessive (type III). IGHD Type 1A classically occurs with homozygous 6.5–45 kb deletions in GH1, which prevent synthesis or secretion of GH. Affected individuals present with severe growth failure before 6 months of age, including a height less than 4.5 standard deviations below the mean [11]. Serum levels of GH are undetectable, and upon initiation of GH replacement therapy, anti-GH antibodies often develop [11]. IGHD Type IB is a less severe autosomal recessive form of GHD resulting from splice site, frameshift, missense, and nonsense mutations in GH1 [11]. IGHD Type II is commonly due to single base deletions from the first six nucleotides of intron 3. This mutation results in the increased production of a 17.5 kDa form of GH. Phenotypic presentations vary as affected individuals may range from having a normal height to exhibiting severe short stature. Other pituitary hormone deficiencies may also develop when splice site mutations are present, including adrenocorticotropic hormone (ACTH), prolactin, thyroid-stimulating hormone (TSH), or gonadotropin deficiencies. A hypoplastic anterior pituitary gland may be detected on MRI in approximately 38–50% of individuals [11]. IGHD Type III may be associated with X-linked mutations, such as SOX3, a transcription factor located at Xq27 and involved in pituitary development. Duplications at Xq26-27 may be associated with intellectual disability along with either IGHD or hypopituitarism. Studies have reported features including panhypopituitarism, anterior pituitary hypoplasia, and an ectopic or undescended posterior pituitary [11].

GHRH binds to growth hormone releasing hormone receptor (GHRHR), a G-protein coupled receptor in somatotrophs. The GHRHR gene is located on chromosome 7p14. Numerous homozygous or compound heterozygous mutations in GHRHR have been linked to IGHD Type IB, including missense, nonsense, splice site, and regulatory mutations as well as deletions. Individuals with GHRHR mutations present clinically with short stature and low serum levels of GH [11].

Table 1 outlines commonly cited transcription factors implicated in multiple pituitary hormone deficiencies, of which GHD may be the first manifestation. Several other transcription factors have been described [14]. Table 2 outlines causes of GH insensitivity.

Kowarski syndrome, characterized by growth retardation resulting from biologically inactive growth hormone was described in 1978 [15]. Affected children have normal or slightly increased GH secretion and pathologically low IGF1 levels, and normal catch-up

growth with GH therapy. More recent studies have reported molecular abnormalities involving a mutant GH molecule [16,17].

Table 1. GH deficiency [18–23].

Gene	Inheritance Pattern	Clinical Features	Pituitary Deficiencies
HESX1	Autosomal dominant or autosomal recessive	Short stature; anterior pituitary gland hypoplasia, ectopic posterior pituitary gland; septo-optic dysplasia, agenesis of the corpus callosum, absent infundibulum	GH, TSH, LH, FSH, PRL, and ACTH deficiencies
POU1F1	Autosomal dominant or autosomal recessive	Short stature; small or normal anterior pituitary gland	GH and PRL deficiencies, usually severe; TSH deficiency variable
PROP1	Autosomal recessive	Short stature, although normal adult heights have been reported even without treatment; possible delayed puberty and infertility	GH, TSH, LH, FSH, and PRL deficiencies; GH, PRL, and TSH deficiencies milder than in patients with POU1F1 mutations; cortisol deficiency increasing with age
LHX3	Autosomal recessive	Short stature; short, rigid cervical spine with restricted neck range of motion; small, normal, or enlarged anterior pituitary gland	GH, TSH, LH, FSH, and PRL deficiencies
LHX4	Autosomal dominant	Short stature; small anterior pituitary gland, ectopic posterior pituitary gland, absent infundibulum, and cerebellum abnormalities (inadequately formed sella turcica and pointed cerebellar tonsils)	GH, TSH, and ACTH deficiencies
GLI2	Autosomal dominant	Short stature; holoprosencephaly and multiple midline defects (single nares, single central incisor); variable craniofacial abnormalities	GH, TSH, LH, FSH, prolactin and ACTH deficiencies
PITX2	Autosomal dominant	Short stature; Rieger syndrome—variable presentation: abnormalities of anterior chamber of eye, dental hypoplasia, protuberant umbilicus, intellectual disability, and pituitary abnormalities	
OTX2	Autosomal dominant	Short stature, anophthalmia, microphthalmia; also possible optic nerve hypoplasia and other eye abnormalities, brain and pituitary abnormalities, developmental delay, intellectual disability, and feeding difficulties	

GH = growth hormone TSH = thyroid stimulating hormone, LH = luteinizing hormone, FSH = follicle stimulating hormone, PRL = prolactin, and ACTH = adrenocorticotropic hormone.

Table 2. GH insensitivity [24,25].

Gene Involved	Inheritance Pattern	Features
GHR	Autosomal recessive or autosomal dominant	Laron syndrome—variable height presentation, midfacial hypoplasia
STAT5B	Autosomal recessive	Midfacial hypoplasia, immunodeficiency, pulmonary insufficiency, elevated PRL
IGFALS	Autosomal recessive	Mild short stature
IPAPPA2	Autosomal recessive	Mild short stature; microcephaly, skeletal abnormalities
IGF1	Autosomal recessive	SGA, microcephaly, intellectual disability, deafness
IGF1R	Autosomal dominant or autosomal recessive	SGA, microcephaly, intellectual disability, insulin insensitivity, decreased bone density
IGF2	Paternal inheritance	SGA, short stature, macrocephaly, triangular facies, frontal bossing, low-set ears, clinodactyly, micrognathia/retrognathia

SGA = small for gestational age, PRL = prolactin.

3. Clinical Presentation

Newborns with congenital GHD can present with hypoglycemia and prolonged jaundice. It is important to note that fetal growth is influenced by genetic and environmental factors, as well as by nutrition and growth factors, including insulin [26]. Growth patterns in infants with congenital GHD vary depending on the severity of the deficiency. One study showed that infants with isolated congenital GHD or multiple pituitary deficiencies, but without any dysmorphic features, have a normal birth weight and length. It is not until 6–12 months of age when these individuals experience linear growth deceleration and their length begins to deviate from the mean [27]. Another study comprised of children with similar inclusion and exclusion criteria found birth length to be decreased in 69% of patients while birth weight and adiposity were relatively increased. More than half of these individuals had isolated GHD, suggesting that other hormone deficiencies were likely not responsible for this reduced birth length. In 61% of patients, length continued to decline further in the postnatal period [28]. In a third study, two distinct growth patterns were observed: the first curve showed a decline in growth starting immediately from birth while the second curve traveled parallel to the normal curve for the first 9 months of life before deviating downwards [29]. This study also concluded that additional hormone deficiencies (TSH, ACTH) could not account for the differing growth patterns between the two groups [29]. The general consensus from these studies is that congenital GHD may present differently depending on the severity of the hormone deficiency. Clinical manifestations of linear growth failure may be apparent immediately from birth in more severe cases or growth abnormalities may not become apparent until 6–12 months of age [27–29]. If there are associated multiple pituitary hormone deficiencies, additional abnormalities can be seen. When combined with gonadotropin deficiency, genitourinary abnormalities such as micropenis and cryptorchidism are seen in males. Breech presentation and post-delivery complications including perinatal asphyxia, bradycardia, and peripheral cyanosis have also been associated with congenital GHD [28,30]. Additional features include changes in body composition (increased peri-abdominal fat, decreased muscle mass), delayed dentition, hair and nail changes, and a high pitched voice.

Acquired GHD may be idiopathic or may arise from a variety of factors affecting the sellar region, including head trauma, tumors, irradiation, surgery, inflammation, infection, or infiltrative conditions that disrupt the pituitary stalk [31–33]. Growth failure is the classic presentation of acquired GHD, although the onset of this may occur rapidly or insidiously depending on the etiology. In the case of tumors, nearly one third of patients experience growth failure as their initial symptom. In traumatic brain injuries, growth failure may present within a few months following injury in some individuals while it may not occur until over a year later in others [34]. Growth deceleration is defined as a growth velocity that is below the 5th percentile for age and gender (e.g., <5 cm/year after the age of 5 years) or a height decrease across two or more percentiles on the growth chart [35].

4. Diagnostic Approach

The diagnostic workup should begin with a thorough history and physical examination. Birth history (maternal health during pregnancy, birth difficulties, mode of delivery, birth weight and length, postnatal complications), review of general health, significant medical and surgical history, and family history (consanguinity, familial heights and age at onset of puberty, medical problems) should be obtained [36]. Clinical information obtained from the history including neonatal hypoglycemia, prolonged neonatal jaundice, or prior cranial irradiation increase suspicion for GHD [37]. In addition to a general examination, evaluation for dysmorphic features, body proportions, and well as Tanner staging should be done [36,38].

Careful assessment of the growth curves is critical. First, it is important to ensure that the measurements are precise and plotted appropriately on the correct chart. The height and its relation to the chronological age as well as the child's genetic potential is important. Mid-parental target height is calculated for girls using (father's height + mother's height

− 13 cm)/2 and in boys using (father's height + mother's height + 13 cm)/2 [39]. The weight-to-height ratio is also important. Endocrine disorders are typically associated with relatively preserved weight gain or obesity in a short child while systemic disorders are associated with greater impairment in weight gain than linear growth. However, most important is the growth velocity, which requires measurements ideally 6 months apart [40].

Initial workup for short stature typically includes a TSH level as well as GH markers (IGF-1 and IGFBP-3), and a karyotype in girls to evaluate for mosaic Turner syndrome as short stature may be the only clinical manifestation [40,41]. Routine laboratory screening for occult disease including a complete blood count (CBC), electrolytes, liver function tests, erythrocyte sedimentation rate (ESR), and celiac testing are also often checked [42]. It is difficult to evaluate GH production directly as its secretion is pulsatile (except in neonates) and its regulation is multifaceted. Although low values of IGF-1 and/or IGFBP-3 raise concerns for GHD, there are limitations to these tests [41]. In very young children less than 3 years of age, there is an overlap in IGF-1 levels when comparing healthy children and those with GHD. In this age group, the IGFBP-3 biomarker may be a more reliable method of evaluation [43,44]. Other causes of low IGF-1 include poor nutrition, chronic illness, and liver disease [41,45]. A bone age X-ray (X-ray of the hand and wrist) is helpful in comparing the chronological age to skeletal age [36]. Bone age is typically delayed in GHD, however this may not be the case in recently acquired GHD, and can even be advanced in patients with severe obesity [46]. The more severe or longstanding the GHD, the greater the difference between the chronological age and bone age [44]. A delayed bone age is not diagnostic of a specific diagnosis and can be seen in many other conditions including hypothyroidism. Bone age imaging can also be helpful in identifying subtle signs of skeletal dysplasia.

GH stimulation testing can be undertaken to aid in the diagnosis of GHD, however is not always required. For example, an infant with a history of neonatal hypoglycemia, prolonged jaundice after birth, midline defects, low IGF-I and IGFBP-3, and/or multiple pituitary hormones deficiencies has sufficient clinical and biochemical evidence to support GHD, and does not require stimulation testing [43]. There are many available testing options. Screening tests using exercise, fasting, or agents such as levodopa or clonidine to stimulate GH secretion, are easy to administer and are low risk. However, they also have low specificity, and are therefore combined or performed sequentially with a second agent such as arginine, insulin, or glucagon. Failure of two tests is diagnostic of GHD [43]. Traditionally, test failure has been defined as a GH level that is less than 10 ng/mL in children [37,47]. However, there is no controlled, evidence-based gold standard for this cutoff and results of stimulation testing should not be used as the sole diagnostic criterion of GHD for many reasons. There is overlap in peak GH concentrations between normal children and those with GHD. Adiposity also influences GH response to stimulation testing, with blunted responses in obese or overweight individuals [47]. Further, there is a need for standardization in testing and agent- and assay-specific reference ranges [48,49]. Another area of controversy is sex steroid priming which involves administering sex steroids prior to the stimulation testing. Sex steroids cause an increase in GH secretion during pubertal development, and therefore advocates of this practice utilize priming to enhance the release of GH in response to the given stimulus in order to decrease the rate of false positives. This technique can be helpful in distinguishing GHD and CDGP, conditions that are difficult to differentiate due to overlapping features [41,44].

MRI imaging of the brain with a focus on the hypothalamus and pituitary gland should be performed in all patients diagnosed with GHD to detect anatomical defects. Absence of the anterior pituitary gland (empty sella), an ectopic posterior pituitary gland, and hypoplasia of the pituitary stalk and/or pituitary gland are supportive of a diagnosis of GHD. Congenital CNS malformations including holoprosencephaly, septo-optic dysplasia, and midline craniocerebral or midfacial abnormalities can be associated with pituitary abnormalities on imaging. Imaging is also important for predicting the likelihood of other pituitary hormone deficiencies, the utility of genetic testing, and the likelihood of persistent GHD [43].

Genetic testing is not performed routinely in the diagnosis of isolated GHD, however can be considered in some cases. In a study evaluating patients and pedigrees with IGHD, approximately 77% of cases were sporadic while the remaining 23% were familial. Mutations in GH1 and GHRHR were discovered in approximately 11% of individuals with IGHD. Rates were higher in familial cases, with a prevalence of nearly 39%, and in consanguineous cases, having a prevalence of 75%. Patients for whom specific mutations had been identified experienced more severe perturbations to their growth than those without identifiable mutations. The authors of this study recommend genetic screening for idiopathic GHD patients who present with severe growth failure and a suggestive family history [50].

5. Treatment

Treatment of GHD is accomplished by administration of recombinant human growth hormone (rhGH). Treatment can be given in children whose epiphyses are open [51]. Historically, treatment has required daily subcutaneous injections typically administered in the evening to more closely match the release pattern of endogenous GH. However, no difference in effectiveness has been observed based on the timing of medication administration [52]. Sustained-release preparations of rhGH are also now available in the United States and a few other countries. In a 52-week randomized study in prepubertal children with GHD, patients using once weekly lonapegsomatropin had an annualized height velocity (AHV) of 11.2 $\pm$ 0.2 cm/year, while patients treated with equivalent doses of aqueous rhGH administered by daily subcutaneous injection had an AHV of 10.3 $\pm$ 0.3 cm/year [53]. This study also found similar safety data in the two groups. Long acting preparations can help with the treatment burden of daily injections and may improve medication adherence.

The growth response is greater when rhGH is initiated at a younger age, and therefore, treatment should be initiated as soon as the diagnosis of GHD is confirmed. In addition to linear growth benefits, GH has an important role in bone health. Children with GHD have a reduced bone mineral density (BMD) and GH treatment has been shown to improve BMD and have a important role in the attainment of peak bone mass in children with GHD [54]. The initial dosing is between 0.16–0.24 mg/kg/week divided into daily injections [47]. For lonapegsomatropin, the approved dosing is 0.24 mg/kg given once weekly for children $\geq$1 year and weight $\geq$11.5 kg. Successive doses may be adjusted depending on individual patient responses to treatment and IGF-1 levels. The Pediatric Endocrine Society guidelines recommend decreasing the dose if IGF-1 levels are above the normal range, as very high levels may be associated with drug toxicity [47].

Treatment with rHGH has potential adverse effects. Acute effects including idiopathic intracranial hypertension (pseudotumor cerebri), slipped capital femoral epiphysis (SCFE), and worsening of existing scoliosis have been reported. Other reported side effects include insulin resistance, musculoskeletal symptoms such as edema, carpal tunnel syndrome, muscular pain related to fluid retention, and pancreatitis. GH can cause tonsillar hypertrophy and exacerbate obstructive sleep apnea and therefore polysomnography is recommended in at risk patients, specifically those with Prader-Willi syndrome. It is important to note that GH treatment can increase metabolism of cortisol and thyroid hormone, and may unmask adrenal insufficiency or hypothyroidism [47,55,56]. Long-term, there are concerns related to cancer risk. The SAGhE study which evaluated a cohort of almost 24,000 patients treated with rhGH did not support a clear carcinogenic effect of rhGH in patients with growth failure without any other major disease, however study limitations were noted including the limited length of follow-up [57].

GH treatment is generally continued until linear growth velocity decreases below 2–2.5 cm/year [47]. Patients should then be retested for GHD to determine if GH should be continued into adulthood, as GH therapy offers benefits in body composition (reduction in fat mass, increase in muscle mass), exercise capacity, skeletal integrity, lipids, and quality of life measures [58].

6. Conclusions

A child with short stature requires a comprehensive evaluation to appropriately differentiate a normal variant of short stature from a pathologic cause such as GHD. There is no gold standard in diagnosing GHD, and no one test supersedes clinical evaluation and judgement. Treatment with rhGH is available in daily and weekly injections for children with GHD and should be initiated as soon as the diagnosis is made. Patients require close monitoring with attention to growth velocity and potential adverse effects. Further data are needed to standardize and revise our diagnostic criteria, specifically standardization of GH stimulation testing protocols and GH cutoff values. Although genetic testing is not routinely done in patients with GHD, it will likely play a greater role in our diagnostic workup in the future.

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