# Childhood Growth Hormone Deficiency and Hypopituitarism

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**Abstract**

Hypopituitarism is the deficiency in varying degrees of one or multiple pituitary hormones. In this chapter, GH deficiency (GHD) will be discussed, while other hormonal deficiencies are presented elsewhere in this book. To understand GHD, an understanding of the GH axis is important and follows below.

**Keywords**

Growth hormone • Growth hormone deficiency • Hypopituitarism • Pituitary

## Introduction

The pituitary gland is formed of anterior (adenohypophysis) and posterior (neurohypophysis) parts, which are embryologically derived from two different sources [1]. The primordium of the anterior pituitary, Rathke's pouch, forms by the upward invagination of the stomodeal ectoderm in the region of contact with the neuroectoderm of the primordium of the ventral hypothalamus [2]. Rathke's pouch can be identified by the third week of pregnancy [3]. The posterior pituitary arises from the neural ectoderm of the forebrain.

The anterior pituitary is formed of three parts, namely the pars distalis (pars anterior or anterior lobe), the pars intermedia (intermediate lobe), and the pars tuberalis (pars infundibularis or pars proximalis), and forms 80% of the pituitary gland. In humans, the pars distalis is the largest part of the anterior pituitary and where most of the anterior pituitary hormones are produced [3]. The intermediate lobe is poorly developed in humans, and although it is only a rudimentary vestige in adults, it is relatively obvious in pregnant women and in the fetus [4]. The upward extension of the pars distalis onto the pituitary stalk forms the pars

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tuberalis, which may contain a small number of gonadotropin-producing cells [3].

Peptides produced in neurons of the hypothalamus are transported via a capillary plexus in the pituitary stalk to the anterior pituitary, where they regulate the release of several hormones that are synthesized there [5]. These hormones are somatotropin or growth hormone (GH), prolactin (PRL), thyrotropin or thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and adrenocorticotropin (ACTH). Posterior pituitary hormones are synthesized in cell bodies of neurons in the hypothalamus and transported along their axons through the neurohypophyseal tract of the pituitary stalk. These hormones, arginine vasopressin or antidiuretic hormone (ADH) and oxytocin, are stored in and secreted from the posterior pituitary [6].

Hypopituitarism is the deficiency in varying degrees of one or multiple pituitary hormones. In this chapter, GH deficiency (GHD) will be discussed, while other hormonal deficiencies are presented elsewhere in this book. To understand GHD, an understanding of the GH axis is important and follows below.

## GH Physiology

### GH Gene

GH, which has a molecular weight of 22 kDa, is a single-chain α-helical non-glycosylated polypeptide with 191 amino acids and two intramolecular disulfide bonds. This mature hormone accounts for 75% of the GH produced in the pituitary gland [3]. There exists a 20-kDa variant form, which arises from alternative splicing during the processing of human GH (hGH) pre-mRNA and constitutes 5–10% of the total pituitary hGH [7, 8]. The remainder of the GH produced by the pituitary is in the *N*-acetylated and desaminated forms and oligomers [3]. Secreted GH circulates both unbound and bound to binding proteins, which are portions of the extracellular domain of the GH receptor (GH-R) [9].

The *GH1* gene encodes for GH and is part of a 50-kb cluster of five genes located on human chromosome 17q22-24: They include *GH1*, *chorionic somatomammotropin* (*CS*)*-like* (*L*), *CS-A*, *GH-2*, and *CS-B* [10]. The CS-L translated protein appears nonfunctional, while CS-A and CS-B encode human chorionic somatomammotropin (hCS) or human placental lactogen. The syncytiotrophoblastic cells produce hCS, which has 85% homology to GH. hCS also contains two disulfide bonds that occur at the same positions as in GH-N, but it only has 0.5% affinity for the GH-R. Interestingly, hCS does not appear necessary for fetal or extrauterine growth nor does it appear essential for maintenance of pregnancy or lactation [11]. The *GH-2* gene product, which is known as GH variant (GH-V), differs from GH-N by 13 amino acids. It is expressed as at least four alternatively spliced mRNAs in the placenta and is continuously secreted during the second half of pregnancy, suppressing maternal pituitary *GH-1* gene function [12, 13].

### GH Secretion (Fig. 1.1)

GH secretion follows a pulsatile pattern, secondary to the antagonistic influences of growth hormone-releasing hormone (GHRH) and somatotropin release-inhibiting factor (SRIF), also known as somatostatin (sst).

GHRH, a 44-amino-acid protein, binds to the GHRH receptor (GHRH-R), which is a G-protein-coupled receptor with seven-transmembrane-spanning domains with three extracellular and three cytoplasmic loops [14]. Activation of the GHRH-R results in an increase in cyclic adenosine monophosphate (cAMP) and intracellular calcium, leading to the activation of protein kinase A (PKA) [15, 16]. PKA phosphorylates and activates cAMP response element-binding protein (CREB), which binds to cyclic AMP (cAMP) response elements in the *GH* promoter to enhance *GH-1* gene transcription [17, 18]. There is also a PKA-dependent, CREB-independent mechanism of *hGH* gene activation by POU1F1 (also known as Pit-1) and CREB-binding protein (CBP) [19].

SRIF, a 14-amino-acid neuropeptide, negatively regulates GH release primarily via the

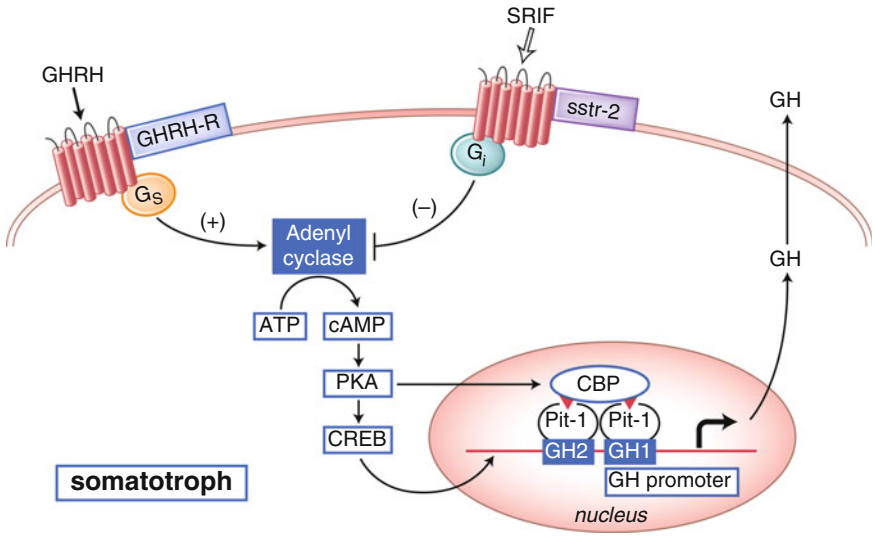


**Fig. 1.1** Simplified model of *growth hormone* (*GH*) gene activation. GH synthesis and release from somatotrophs is regulated by growth hormone-releasing hormone (GHRH) stimulation and somatostatin (SRIF) inhibition. GHRH activation of its Gs-protein-coupled receptor leads to an increase in cyclic adenosine monophosphate (cAMP) and intracellular calcium, resulting in activation of protein kinase A (PKA). PKA phosphorylates and activates cAMP response element-binding protein (CREB), which binds to cAMP response elements in the *GH* promoter to enhance *GH1* gene transcription. There is also a PKA-dependent, CREB-independent mechanism of human *GH* gene activation by Pit-1 and CREB-binding protein (CBP). SRIF activation of its Gi-coupled protein leads to a decrease in cAMP and a reduction in calcium influx

SRIF receptor subtype 2 (sstr2) [20]. SRIF activates a $G_i$-coupled protein [21, 22], which decreases cAMP and reduces calcium influx, resulting in inhibition of GH secretion [23]. SRIF controls the pulse frequency of GH [24, 25].

Infants have nonpulsatile GH secretion. There is a gradual increase in 24-h integrated GH secretion during childhood. The amplitudes of GH pulses are increased during puberty, which is probably secondary to the effect of gonadal steroids on GHRH [26–28]. Although hGH production continues throughout life, the levels decline in the elderly [29, 30].

Synthetic hexapeptides capable of stimulating GH secretion are termed GH secretagogues (GHS) or GH-releasing peptides (GHRP); these compounds can stimulate GH release but do not act through the GHRH or SRIF receptors [31, 32]. These peptides can initiate and amplify pulsatile GH release; however, this is accomplished via the GHS receptor (GHS-R), which is distinct from the GHRH-R [33]. The GHS-R is a seven-transmembrane G-protein-coupled receptor that acts via protein kinase C activation and is expressed in the hypothalamus and in pituitary somatotrophs [34].

An endogenous ligand for the GHS-R named ghrelin has been identified and has been shown to stimulate GH release in a dose-related manner, as well as potentiate GHRH-dependent secretion of GH [35, 36]. It is produced mainly by the oxyntic cells of the stomach but is also found throughout the gastrointestinal tract, as well as in the hypothalamus, heart, lung, and adipose tissue [37]. Several studies have demonstrated that ghrelin has a wide range of effects, including acting as a physiological mediator of feeding [38, 39]. Thus, it is difficult to separate the direct effects of ghrelin from those related to GH secretion.

## GH Action (Fig. 1.2)

Approximately 50% of circulating GH is bound to GH-binding protein (GHBP). GHBP is produced in multiple tissues, with liver the

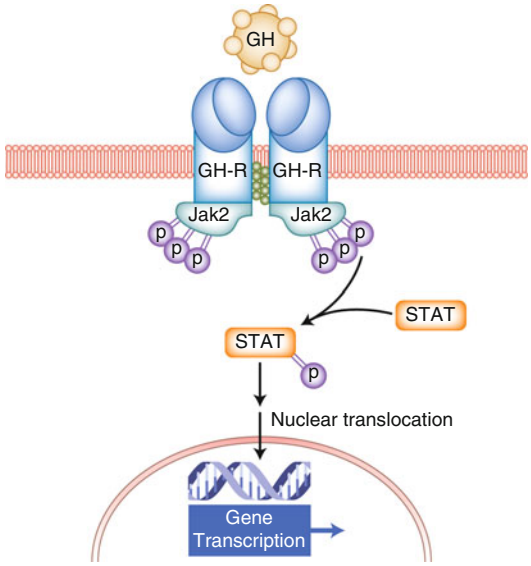


**Fig. 1.2** Schematic model of growth hormone receptor (GH-R) binding and signaling. A single GH molecule binds asymmetrically to the extracellular domain of two receptor molecules, causing a conformational change. This leads to interaction of the GH-R with Janus kinase (Jak 2) and tyrosine phosphorylation of both Jak2 and GH-R, followed by phosphorylation of cytoplasmic transcription factors known as signal transducers and activators of transcription (STATS). After phosphorylation, STATs dimerize and move to the nucleus, where they activate gene transcription

predominant source. GHBP acts as a circulating buffer or reservoir for GH, prolonging the half-life of plasma GH and competing with the GHR for GH, probably forming an unproductive heterodimer.

In general, GHBP levels reflect GH-R levels and activity, yet its source or mechanism of generation is not entirely known. In rodents, it appears to be synthesized de novo from alternative splicing of *GH-R* mRNA. In humans, rabbits, and others, it may be shed from membrane-bound GH-R by proteolytic cleavage [9, 40].

The GH-R is a 620-amino-acid protein that belongs to the cytokine family of receptors [41]. It consists of a large extracellular domain, a single transmembrane helix, and an intracellular domain [42]. The highest level of *GHR* expression is in the liver, followed by muscle, fat, kidney, and heart. GH binds to a homodimer complex of the GHR in order to activate its intracellular signaling pathways. Although dimerization of the GHR was thought to occur after GH binding, recent data demonstrate that the subunits of the GH-R are constitutively dimerized in an unbound or inactive state [43, 44]. The GH-binding sites on the extracellular domains of the two subunits are placed asymmetrically; GH binding to the constitutive dimer induces rotation of the two subunits that is transmitted via the transmembrane domain to the intracellular domain, allowing downstream kinase activation by phosphorylation of Janus kinase 2 (Jak2) [44]. Subsequently, the JAK2 molecule causes phosphorylation of critical tyrosines on the intracellular portion of the GH-R, which then provide docking sites for critical intermediary signal transducers and activators of transcription (STAT) proteins [45–47]. After phosphorylation, STATs dimerize and move to the nucleus, where they activate gene transcription [48, 49].

Many of the actions of GH, both metabolic and mitogenic, are mediated by insulin-like growth factors (IGFs) or somatomedins, initially identified by their ability to incorporate sulfate into rat cartilage [50]. IGF-1, which is a basic 70-amino-acid peptide, is produced under the direction of GH predominantly in the liver [51]. It plays an important role in both embryonic and postnatal growth. Both systemic and local IGF-1 have been shown to stimulate longitudinal bone growth by increased osteoblast activity and increased synthesis of collagen [52–56].

Human fetal serum IGF-1 levels, which are approximately 30–50% of adult levels, have been positively correlated with gestational age [57, 58]. The levels of IGF-1 gradually increase during childhood and peak during pubertal development, achieving 2–3 times the normal adult values [59, 60]. IGF-1 production is also augmented by the rise in gonadal steroids, which contribute to the pubertal growth spurt. After adolescence, serum IGF-1 concentrations decline gradually with age [61, 62]. IGFs circulate within the plasma complexed to high-affinity binding proteins or IGF-binding proteins (IGFBPs). IGFBPs extend the serum half-life of IGFs, transport IGFs into target cells, and modulate the interaction of IGFs with their receptors [63, 64]. Six distinct human and rat

IGFBPs have been cloned and sequenced [65, 66]. IGFBP-3, which is GH dependent, is the major IGFBP in human serum and transports over 90% of the circulating IGF-1 [3].

The IGF-I receptor (IGF-1R), which is structurally related to the insulin receptor, is a heterotetramer comprised of two-membrane-spanning α (alpha) subunits and two intracellular β (beta) subunits [67, 68]. The subunits are linked by disulfide bonds and contain binding sites for IGF-I. The subunits are composed of a transmembrane domain, an adenosine triphosphate (ATP)-binding site, and a tyrosine kinase domain that mediates the presumed signal transduction mechanism for the receptor [3, 69].

## Growth Hormone Deficiency

Hypopituitarism can be caused by anything that damages the hypothalamus, pituitary stalk, or pituitary gland. The incidence of congenital GH deficiency has been reported as between 1:4,000 and 1:10,000 live births [70, 71]. Growth failure presenting in infancy and childhood is the most common sign of GH deficiency. Children with mild GH deficiency usually present after 6 months of age when the influences of maternal hormones wane [72]. They generally have normal birth weights and lengths slightly below average [73]. The growth rate of a child with GH deficiency will progressively decline, and typically the bone age will be delayed. They develop increased periabdominal fat [74] and decreased muscle mass and may also have delayed dentition, thin hair, poor nail growth, and high-pitched voice [72]. Severe GH deficiency in the newborn period may be characterized by hypoglycemia and conjugated hyperbilirubinemia, as well as a small phallus in boys, consistent with multiple anterior pituitary hormone deficiencies [72].

## Congenital Forms of Hypopituitarism (Table 1.1)

Congenital cranial malformations, including holoprosencephaly, septo-optic dysplasia (SOD), and midline craniocerebral or midfacial abnormalities, can be associated with anomalies of the pituitary gland. These embryonic defects also include pituitary hypoplasia, pituitary aplasia, and congenital absence of the pituitary gland [6]. Clinically, they may be associated with pituitary hormone deficiencies or the risk for developing future hormone deficiencies. Although these conditions often have no identifiable etiology, ongoing advances in understanding pituitary development have provided a genetic basis to account for pituitary pathology. Mutations have been found in genes necessary for pituitary development and function. The following presents a summary of reported genetic defects associated with pituitary pathology.

**Table 1.1** Congenital causes of or associations with growth hormone deficiency

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| Cranial and central nervous system abnormalities |
| Septo-optic dysplasia |
| Cleft lip ± palate |
| Empty sella syndrome |
| Holoprosencephaly, anencephaly |
| Pituitary aplasia or hypoplasia |
| Thin or absent pituitary stalk |
| Hydrocephalus |
| Genetic (mutations, deletions) |
| GRHR receptor |
| Pituitary transcription factors |
| Hesx1 (Rpx) |
| Ptx2 (Pitx2, P-OTX2, Rieg) |
| Lhx3 (Lim-3, P-LIM) |
| Prop1 |
| POU1F1 (Pit-1, GHF-1) |
| GH-1 |
| Types Ia, Ib, II, and III |
| Multiple GH family gene deletions |
| Bioinactive GH |
| GH receptor |
| IGF-1 |
| IGF-1 receptor |
| Stat 5b mutations |
| Idiopathic |

*GHRH receptor* (*GHRH-R*) *mutations*: Mutations reported in the GHRH-R are often classified as a type of isolated GH deficiency. The little mouse (*lit*/*lit*), which demonstrates dwarfism and decreased number of somatotrophs, has a recessively inherited missense mutation in the extra-

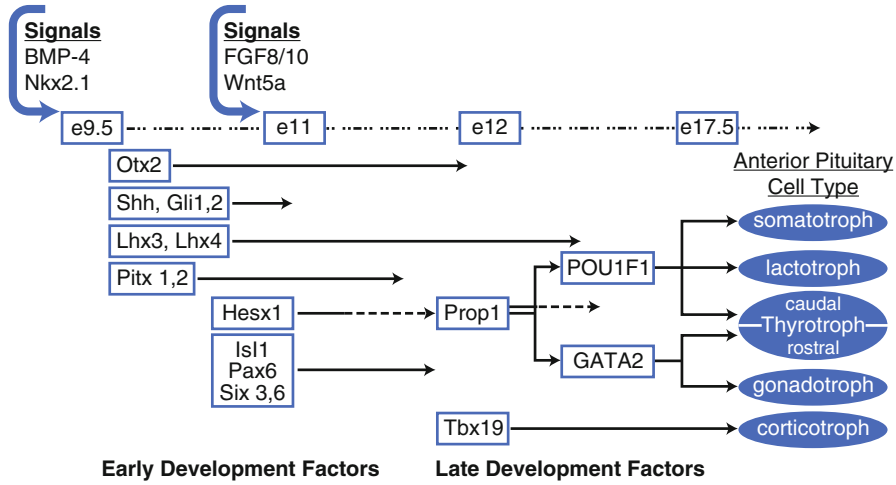


**Fig. 1.3** Anterior pituitary development. The development of the mature pituitary gland initiates with the contact of the oral ectoderm with the neural ectoderm followed by a cascade of events consisting of both signaling molecules and transcription factors expressed in a specific temporal and spatial fashion. This figure presents a modified overview of pituitary development adapted from previous embryological studies performed in murine species by illustrating the temporal expression of various developmental factors. Early on, bone morphogenic protein 4 (BMP-4) and Nkx2.1 are expressed along with sonic hedgehog (Shh) in order to form the primordial Rathke's pouch, which will become the mature pituitary. Also expressed are Gli1 and 2, Lhx3, and Pitx1 and 2, which all play a role in the development of progenitor pituitary cell types. Subsequently, the expression of Hesx1, Isl1, paired box gene 6 (Pax6), and Six3 assists in appropriate cellular development, proliferation, and migration. The *hashed arrows* denote the attenuation of an expressed factor, such as seen with Hesx1, and are often required for the expression of another factor. The attenuation of Hesx1, for example, is required for the expression of Prop1. Similarly, POU1F1 (Pit-1), which is required for somatotroph, lactotroph, and thyrotroph development, is expressed upon the attenuation of Prop1 expression. Ultimately, the mature pituitary gland is marked by the differentiated cell types: somatotrophs, lactotrophs, thyrotrophs, gonadotrophs, and corticotrophs [121, 267, 268]

cellular domain of the gene for *Ghrhr* [75, 76, 77]. In addition to GH deficiency, these mice exhibit postnatal growth failure and delayed pubertal maturation [77]. In humans, two cousins presented clinically with the typical phenotype of severe GHD and were found to have a nonsense mutation in the human *GHRH-R* gene that introduced a stop codon at position 72 (E72X) [78]. A similar mutation is found in codon 50 in "Dwarfism of Sindh" [79].

*Pituitary transcription factor mutations*: Normal development of the pituitary is a complex cascade of events that has been shown to be dependent on several pituitary-specific transcription factors, which are expressed in a specific spatial and temporal pattern. The coordination of expression of these factors ultimately leads to the development of the pituitary-specific cell types (Fig. 1.3). Although mutations in these factors are often rare, it is important for the clinician to recognize the genetic basis for the pathology of idiopathic hypopituitarism. The genetic evaluation of patients diagnosed with idiopathic hypopituitarism has identified mutations in these factors accounting for pituitary dysfunction.

*HESX1* (*Rpx*): HESX1, a member of the paired-like class of homeobox genes originally described in *Drosophila melanogaster*, is one of the earliest known specific markers for the pituitary primordium [80, 81], although no target genes for Rpx have yet been identified [82]. Hesx1 null mutant mice demonstrate abnormalities in the corpus callosum, anterior and hippocampal commissures, and septum pellucidum, presenting a similar phenotype to defects seen in humans with SOD [80]. Two siblings with agenesis of the corpus callosum, optic nerve hypoplasia, and panhypopituitarism were found to have a homozygous

mutation at codon 53 (arginine to cysteine) in the homeodomain (DNA-binding domain) of *HESX1*, resulting in a drastic reduction in DNA binding [80]. More recently, a novel I26T mutation in exon 1 was reported in a patient with early GHD, FSH/LH deficiency, and evolving TSH and cortisol deficiency, along with pituitary structural abnormalities but normal optic nerves [83].

Several investigators have organized screenings to assist in identifying mutations in *HESX1*. Thomas et al., for example, scanned 228 patients with a wide spectrum of congenital hypopituitarism phenotypes: 85 with isolated pituitary hypoplasia [including isolated GH deficiency and combined pituitary hormone deficiency (CPHD)], 105 with SOD, and 38 with holoprosencephaly or related phenotypes. In this cohort, three missense mutations were identified [84]. More recently, approximately 850 patients were studied for mutations in *HESX1* (300 with SOD; 410 with isolated pituitary dysfunction, optic nerve hypoplasia, or midline brain anomalies; and 126 patients with familial inheritance). Only 1% of the group was found to have coding region mutations, suggesting that mutations in *HESX1* are a rare cause of hypopituitarism and SOD [85].

*Ptx2* (*Pitx2*): Ptx2 is a paired-like homeodomain transcription factor closely related to the mammalian *Otx* genes that are expressed in the rostral brain during development and are homologous to the *Drosophila orthodenticle* (*otd*) gene, which is essential for the development of the head in *Drosophila melanogaster* [86]. Ptx2 null mice showed embryonic lethality; however, a hypomorphic allele model of Ptx2 demonstrated pituitary hypoplasia and cellular differentiation defects in proportion to the reduced dosage of Ptx2. The gonadotrophs were most severely affected, followed by somatotrophs and thyrotrophs [87–89].

RIEG is the human homologue of Ptx2, and clinical mutations of PTX2 have been described in patients with Axenfeld-Rieger syndrome. This syndrome is an autosomal dominant condition with variable manifestations including anomalies of the anterior chamber of the eye, dental hypoplasia, a protuberant umbilicus, mental retardation, and pituitary alterations [90]. One group of investigators described mutations in six out of ten families with autosomal dominant Rieger syndrome [91, 92]. Five of the six mutations reported were in the homeobox region, and several show loss of DNA-binding capacity.

*Lhx3* (*Lim-3*, *P-Lim*): Lhx3 is a LIM-type homeodomain protein expressed in the anterior and intermediate lobes of the pituitary gland, the ventral hindbrain, and the spinal cord [93–95]. Lhx3 expression persists in the adult pituitary, suggesting a maintenance function in one or more of the anterior pituitary cell types [93]. In addition, its expression is associated with cells that secrete GH and PRL, as well as the expression of the α-glycoprotein subunit (α -GSU), suggesting a common cell precursor for gonadotrophs, thyrotrophs, somatotrophs, and lactotrophs [93, 96].

In humans, homozygous loss-of-function mutations in LHX3 have been identified in patients with hypopituitarism including GH, TSH, PRL, LH, and FSH deficiencies, anterior pituitary defects, and cervical abnormalities with or without restricted neck rotation [97–99]. Among 366 studied patients with IGHD or CPHD, only 7 patients from 4 families were found to have LHX3 mutations, suggesting *LHX3* mutations are a rare cause of CPHD [99].

*Prop1*: Prop1 is a paired-like homeodomain transcription factor with expression restricted to the anterior pituitary during development [2, 100]. During pituitary development, Prop1 acts as a repressor in downregulating Hesx1 and as an activator of POU1F1 [101]. A considerable variation in clinical phenotypes of patients with PROP1 mutations has been demonstrated, even in patients bearing identical genotypes [100, 102, 103]. Several reports have shown that hormone deficiency may be variable and dynamic; some patients may develop cortisol deficiency over time or hypogonadotrophic hypogonadism despite the progression into spontaneous puberty [100, 104–106].

Multiple nonconsanguineous patients from at least eight different countries have a documented recurring homozygous autosomal recessive mutation of PROP1, delA301,G302 (also known as

296delGA) in exon 2, which changes a serine to a stop codon at codon 109 in the homeodomain, resulting in a truncated gene product [107–109]. In one family, progressive ACTH deficiency was noted with age [110]. In another consanguineous Indian pedigree, a 112-124del mutation resulting in a premature stop codon at position 480 was identified, and in addition to GH, PRL, TSH, and gonadotropin deficiencies, affected individuals were also noted to have an impaired pituitary-adrenal axis [111]. Several other mutations in PROP1 have been described [100, 107, 112–114].

*Pou1f1*: Pou1f1 (*PIT-1*, GHF-1) is a member of a family of transcription factors, POU, which are responsible for mammalian development and its expression is restricted to the anterior pituitary lobe [115, 116]. Pit-1 has been shown to be essential for the development of somatotrophs, lactotrophs, and thyrotrophs, as well as for their cell-specific gene expression and regulation [116].

Mutations in *POU1F1* in humans were described in 1992 by four different groups in patients with CPHD consisting of GHD, TSH, and PRL deficiencies and variable hypoplastic anterior pituitaries on MRI [117–120]. At least 28 different mutations have been described, with 23 demonstrating autosomal recessive inheritance and five demonstrating dominant inheritance [121]. The most common mutation is an R271W substitution affecting the POU homeodomain; this leads to a mutant protein that binds normally to DNA but acts as a dominant inhibitor of transcription and may act by impairing dimerization [118, 120, 122–129].

In another single allele mutation, K216E, the mutant Pit-1 is able to bind DNA, but unable to support retinoic acid induction of the *Pit-1* gene distal enhancer either alone or in combination with wild-type Pit-1. This ability to selectively impair the interaction with the superfamily of nuclear hormone receptors is another mechanism responsible for CPHD [130]. Several other point mutations in the Pit-1 gene resulting in CPHD have been described. Some alter residues important for DNA binding and/or alter the predicted α-helical nature of the Pit-1, while others have been shown to or postulated to impair transactivation of target genes [121, 131].

*Isolated GHD* (*IGHD*): Four forms of IGHD have been described, and its classification is based upon the clinical presentation, inheritance pattern, and GH secretion.

*IGHD Type IA* results primarily from large deletions along with microdeletions and single base pair substitutions of the *GH1* gene, which ultimately prevents synthesis or secretion of the hormone. This condition is associated with growth retardation in infancy and subsequent severe dwarfism. Heterogeneous deletions of both alleles ranging from 6.7 to 45 kb have been described [132–135]. These patients frequently develop antibodies to exogenous GH therapy, which is attributed to the lack of immune tolerance because of prenatal GHD [136, 137]. Some patients may eventually become insensitive to GH replacement therapy demonstrating a decreased clinical response; subsequently, recombinant IGF-1 therapy may be an alternative option.

*IGHD Type IB* is a less severe autosomal recessive form of GHD resulting from mutations or rearrangements of the *GH1* gene, such as splice site mutations that lead to partial GH deficiency [133, 138, 139]. In one study, a homozygous splice site G to C transversion in intron 4 of the *GH-1* gene was identified, causing a splice deletion of half of exon 4 as well as a frame shift within exon 5. These changes ultimately affected the stability and biological activity of the mutant GH protein [140]. Several other deletions or frame shift mutations have been described by others [141–143].

*IGHD Type II* is an autosomal dominant condition considered the most common genetic form of IGHD. Several patients have been found to have intronic transitions in intron 3, inactivating the donor splice site of intron 3 and deleting exon 3 [139, 140, 144–148].

*IGHD Type III* is a partial GH deficiency with X-linked inheritance due to interstitial Xq13.3-Xq21.1 deletions or microduplications of certain X regions. Patients may also have hypogammaglobulinemia, suggesting a contiguous Xq21.2-Xq22 deletion [149, 150].

*Bioinactive GH* has been reported in patients with short stature demonstrating normal GH immunoreactivity but reduced biopotency. A child, with an autosomal arginine to cysteine mutation at codon 77, was described with severe growth retardation, high serum GH levels, elevated GHBP, low IGF-1 levels, and increased GH levels after provocative testing. The child expressed both mutant and wild-type GH; however, the mutant GH had a higher affinity for GHBP, a lower phosphorylating activity, and an inhibitory or dominant negative effect on wild-type GH activity [151]. In another patient, an aspartic acid to lysine mutation at codon 112 was identified and suggested to prevent appropriate GH-R dimerization [152].

There are also patients with the phenotype of growth hormone insensitivity who do not demonstrate mutations of the GH-R gene, but have identified mutations in downstream GH-R signaling molecules. Homozygous mutations in the Stat5b gene, a major GH-dependent mediator of IGF-I gene transcription, have been identified as a cause of GH insensitivity [153, 154]. The first mutation characterized was a point mutation resulting in a marked decrease in phosphorylation of tyrosine [153], a critical step in the pathway to STAT activation of IGF-1 gene transcription; while the second characterized mutation was an insertion in exon 10, leading to early protein termination [154–156]. In addition to growth retardation, both patients had evidence of immune dysfunction presumably because Stat5b is involved in downstream signaling for multiple cytokines.

*GH-R mutations*: Laron dwarfism is an autosomal recessive disorder characterized by clinical features of severe GH deficiency along with low IGF-1 levels but with normal to high levels of GH after provocative testing [157]. Several deletions and point mutations of several GH-R exons have been described [158–167]. Many of these mutations affect the extracellular domain and, therefore, lead to absent or decreased levels of GHBP [168]. Recombinant IGF-1 therapy has been demonstrated to effectively treat these patients [169, 170]. It has also been hypothesized that some patients with idiopathic short stature, normal GH secretion, and low serum concentrations of GHBP may have partial insensitivity to GH due to mutations in the *GH-R* gene [162].

*IGF-1 and IGF-1R mutations*: A patient noted to have a homozygous partial IGF-1 gene deletion with undetectable levels of IGF-1 presented with severe prenatal and postnatal growth failure, bilateral sensorineural deafness, mental retardation, moderately delayed motor development, and behavioral difficulties. His evaluation did not demonstrate a significant delay in his bone age, and an IGFBP-3 level was normal [171].

Studies with African pygmies demonstrate normal levels of hGH, but decreased IGF-1 levels and unresponsiveness to exogenous hGH. Although IGF-1 deficiency has been hypothesized, Bowcock et al. found no differences in restriction fragment length polymorphisms in the IGF-1 gene in Pygmy versus non-Pygmy black Africans [172]. Furthermore, Pygmy T cell lines show IGF-1 resistance at the receptor level with secondary GH resistance [173, 174]. In a recent study, it was demonstrated that adult Pygmies demonstrate a reduction in both GH gene expression (1.8-fold) and GH-R gene expression (8-fold). This decrease of the GH-R expression in Pygmies was associated with reduced serum levels of IGF-I and GHBP [175].

Abnormalities in the IGF-1R gene have also been reported and are often associated with intrauterine growth retardation (IUGR). Several heterozygous mutations of the IGF-1R gene, as well as an association with deletions in chromosome 15q, have been reported in patients with growth retardation [176–181]. The majority of these reported patients carried the diagnosis of IUGR along with progressive postnatal growth retardation; however, other phenotypic characteristics not universal in these patients included findings of developmental delay, microcephaly, or skeletal abnormalities. In addition, IGF-1 levels were found to be either normal or high, whether at baseline or after provocative testing.

Other patients are suspected to have IGF-1 resistance, as they have elevated GH levels and elevated IGF-1 levels [182–184]. In one patient, cultured fibroblasts had a 50% reduction

in IGF-1 binding capacity [183]. Another patient had a markedly diminished ability of IGF-1 to stimulate fibroblast α (alpha)-aminoisobutyric acid uptake compared to control subjects [184]. Their birth lengths, which were less than the fifth percentile, suggest the importance of IGF-1 in fetal growth.

Other post-signal transduction defects and mutations in IGF-binding proteins may occur but have not been demonstrated as of yet.

## Acquired Forms of Hypopituitarism (Table 1.2)

Head trauma can damage the pituitary stalk and infundibulum and lead to the development of transient and permanent diabetes insipidus, as well as other hormonal deficiencies [185, 186]. There are a number of reports suggesting an association between hypopituitarism and a complicated perinatal course, especially breech delivery [70, 187, 188]. It is not clear if a complicated perinatal course causes hypopituitarism or if a brain anomaly leads to both a complicated delivery and hypopituitarism. The finding that some of these patients have a microphallus at birth suggests that pituitary dysfunction may precede the birth trauma [6].

**Table 1.2** Etiologies of acquired growth hormone deficiency

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| Trauma |
| Head injury |
| Perinatal events |
| Infiltrative and autoimmune diseases |
| Langerhans histiocytosis |
| Sarcoidosis |
| Lymphocytic hypophysitis |
| Infections |
| Meningitis |
| Granulomatous diseases |
| Metabolic |
| Hemachromatosis |
| Cerebral edema |
| Neoplasms |
| Craniopharyngioma |
| Germinoma |
| Hypothalamic astrocytoma/optic glioma |
| Cranial irradiation |

Infiltrative conditions can also disrupt the pituitary stalk. Diabetes insipidus can be the first manifestation of Langerhans cell histiocytosis [189–191] or sarcoidosis [192]. Lymphocytic hypophysitis, usually in adult women in late pregnancy or the postpartum period, can result in hypopituitarism [193].

Metabolic disorders can cause hypopituitarism through destruction of the hypothalamus, pituitary stalk, or pituitary. Hemochromatosis is characterized by iron deposition in various tissues, including the pituitary. It may be idiopathic or secondary to multiple transfusions (e.g., for thalassemia major); gonadotropin deficiency is the most common hormonal deficiency, but GHD has also been described [194, 195].

Hypothalamic or pituitary tissue can also be destroyed by the mass effect of suprasellar tumors or by their surgical resection. These tumors include craniopharyngiomas, low-grade gliomas/hypothalamic astrocytomas, germ-cell tumors, and pituitary adenomas [196]. Treatment of brain tumors or acute lymphoblastic leukemia (ALL) with cranial irradiation may also result in GHD. Lower radiation doses preserve pharmacologic response of GH to stimulation, but spontaneous GH secretion may be lost [197]. Discordancy between failure to provoke an adequate GH response to insulin-induced hypoglycemia but normal response to exogenous GHRH stimulation suggested that the hypothalamus is more vulnerable than the anterior pituitary [198]. More recent data, however, from Darzy et al. show that spontaneous GH secretion is maintained in adults after low-dose cranial RT, suggesting there is not GHRH deficiency. There is a normal but decreased peak GH response to stimulation testing indicating decreased somatotroph reserve. They postulate that there is compensatory increase in hypothalamic stimulatory input (GHRH) and suggested that "neurosecretory dysfunction" after low-dose cranial RT may only be seen in puberty during time of increased GH demand [199].

The higher the radiation dose, the more likely and the earlier GHD will occur after treatment [200, 201]. Clayton et al. reported that 84% of children who received greater than 30 Gy to the hypothalamic-pituitary area had evidence of GH deficiency more than 5 years after irradiation

[200]. Higher doses also increase the likelihood of the development of other anterior pituitary hormone deficiencies as well [201]. Cranial radiation can also be associated with precocious puberty, leading to premature epiphyseal fusion [197], and spinal irradiation can lead to skeletal impaired spinal growth [202], both of which will further compromise adult height.

## Diagnosis of Growth Hormone Deficiency

There is much debate as to the proper methods to diagnose GHD in childhood. It is clear that there is a spectrum of GHD and the clinical presentation varies with the degree of hormonal deficiency. In 2000, the Growth Hormone Research Society published its consensus guidelines on the diagnosis and treatment of GHD in childhood and adolescence [203]. In considering who should undergo evaluation for GHD, they stress the importance of first excluding other causes of growth failure and then assessing the patients for clinical features that can coexist with GHD. These features include hypoglycemia, prolonged jaundice, microphallus, and traumatic delivery in the neonate, as well as a history of cranial irradiation, head trauma, and central nervous system infection; family history of GHD and craniofacial midline abnormalities; and presence of other pituitary hormone deficiencies. When present, the majority of these features are seen in patients on the severe end of the spectrum of GHD. These patients are typically easy to diagnose and have low growth velocity and biochemical markers of GHD, including low IGF-1 levels [204] and low peak GH levels after stimulation tests [205].

The majority of patients with GHD will present with short stature without any of these other features. Some suggested guidelines for further evaluation include height more than 3 SD below the population mean, height more than 2 SD below the population mean with a growth velocity more than 1 SD below the mean, or a very low growth velocity (less than minus 2 SD) irrespective of current height [203]. Conventionally, the gold standard for the diagnosis of GHD has been a peak serum GH <10 ng/mL after two different GH stimulation tests. This cutoff is completely arbitrary and has increased from <3 to <10 ng/ml as the supply of GH has increased with the production of recombinant hGH (rhGH). However, the sensitivity and specificity of these tests are limited due to their dependence on physiological parameters such as age, gender, and body weight; the implementation of different pharmacological stimuli; the arbitrary cutoff values; the poorly reproducible results; and the use of different laboratory techniques for the measurement of GH. Assessment of serum levels of IGF-I and its binding protein IGFBP-3 is a major advance in the diagnosis of GH deficiency. Ultimately, the diagnosis is based on the integration of auxological, biochemical, and radiographic criteria.

### Growth Hormone Stimulation Tests

GH is secreted episodically, mostly during slow-wave sleep. Between the pulses of pituitary GH secretion, serum concentrations are typically low, even in GH sufficient children. Radioimmunoassays (RIAs) and immunometric assays are the most commonly used laboratory techniques for determination of GH levels. Estimations performed by RIA use polyclonal antibodies, which render low specificity and higher GH levels when compared with the more specific immunoradiometric assays using two highly specific monoclonal antibodies. Discrepancies up to two- to fourfold have been reported among different assays [206].

A variety of pharmacological tests have been implemented to assess the GH secretory capacity of the pituitary gland [207]. They are expensive, not free of side effects, and require fasting conditions as high glucose levels inhibit GH secretion. GH provocative tests have been divided into two groups: screening tests including exercise, levodopa, and clonidine, and definitive tests including arginine, insulin, and glucagon. Due to their low specificity and sensitivity, and to exclude normal children who might fail a single stimulation test, the performance of two different provocative tests, sequentially or in combination, has been implemented [208, 209]. An inappropriate low secretory response in the second test supposedly is

confirmatory of GH deficiency. However, multiple studies have shown that children diagnosed with isolated GHD based on peak GH levels <10 ng/mL will have normal GH secretion on retesting both in childhood [210] and as adults [211, 212].

Furthermore, in normal children, serum levels of GH are age and sex dependent and show a sharp pubertal increase. Immediately before puberty, GH secretion may normally be very low, making the discrimination between GHD and constitutional delay of growth and puberty difficult. Sex steroid priming with estrogen [213] or androgen [214] to Tanner stage I or II children has been recommended to distinguish between GHD and constitutional delay in growth and puberty [215], although there is no consensus on this recommendation. While children with GHD might have an attenuated response, those with constitutional growth delay will have a normal secretory pattern. In a study by Marin et al. [215], 61% of normal-stature prepubertal children who were not primed with sex steroids failed to raise their peak serum GH concentration above 7 ng/mL following a provocative test.

In summary, the threshold to define GH deficiency to various provocative stimuli is arbitrary and based on no physiological data. Pharmacological tests involve the use of potent GH secretagogues, which may not reflect GH secretion under physiological circumstances, masking the child with partial GH deficiency. GH stimulation tests are reliable only in the diagnosis of severe or complete GH deficiency. In addition to their low reproducibility [216], a "normal" secretory response does not exclude the possibility of various forms of GH insensitivity or partial GH deficiency. Caution must be taken in obese children who undergo provocative testing for GH secretion, due to a negative impact of adipose tissue on GH secretion [217, 218].

## Physiologic Assessment of Growth Hormone Secretion

In addition to pharmacological tests of growth hormone secretion, exercise testing has been implemented as a screening test for GHD, as exercise induces an increase in GH levels. Although it is simple, safe, and inexpensive, up to one-third of normal children have an absent GH response [219]. Additionally, frequent blood sampling can be performed overnight to test for spontaneous GH secretion. The term GH neurosecretory dysfunction refers to patients with an abnormally slow growth rate and low integrated GH concentration (mean serum 24-h GH concentration) but appropriate GH response to provocative tests [220, 221]. The pathophysiology and the incidence of this condition remain unknown. Although the integrated GH concentration has better reproducibility compared to the standard provocative tests, there is still significant intraindividual variation and overlapping with the values found in normal short children [222]. Lanes et al. reported decreased overnight GH concentrations in 25% of normally growing children [223]. As sampling is required every 20 min for a minimum of 12–24 h, this test is not practical for routine clinical care.

GH induces the expression of IGF-I in liver and cartilage. The use of age and puberty-corrected IGF-1 levels has become a major tool in the diagnosis of GHD [224]. Because of little diurnal variation, their quantification in random samples is useful. However, sensitivity is still limited due to a significant overlap with normal values. Low levels of IGF-I may be found in normal children, especially in those less than 5 years of age. Similarly, low levels are reported in children with malnutrition, hypothyroidism, renal failure, hepatic disease, and diabetes mellitus. Serum levels of IGF-I do not correlate perfectly with GH status as determined by provocative GH testing [225, 226].

IGFBP-3 is the major carrier of IGF-1 [227]. It is GH dependent but has less age variation and is less affected by the nutritional status compared to IGF-I and, thus, may correlate more accurately with GH status [228]. Although low levels of IGFBP-3 are suggestive of GH deficiency, up to 43% of normal short children have been reported to have low concentrations [229]. Similarly, normal values have been reported in children with partial GHD [225, 230].

Determinations of IGF-I and IGFBP-3 are reliable tests in the diagnosis of severe GH deficiency and have better reproducibility when compared with GH provocative tests. However, their sensitivity and specificity are still suboptimal [205]. The combination of a low growth velocity and IGF-I level is quite sensitive and specific for the diagnosis of GHD and may remove the need for provocative testing in patients [231] where other causes for growth failure, especially malnutrition and gastrointestinal illness, have been excluded.

## Bone Age Evaluation

The evaluation of skeletal maturation is crucial in the assessment of growth disorders, as osseous growth and maturation is influenced by nutritional, genetic, environmental, and endocrine factors. Skeletal maturation is significantly delayed in patients with GHD, hypothyroidism, hypercortisolism, and chronic diseases. Children with constitutional growth delay will show a delayed bone age, which corresponds with the height age.

In children over 1 year of age, the radiograph of the left hand is commonly used to evaluate the skeletal maturation. The skeletal age or bone age (BA) is determined by comparing the epiphyseal ossification centers with chronological standards from normal children. Comparison of the distal phalanges renders better accuracy. Several methods to determine the BA are available, with the Greulich and Pyle [232] and Tanner-Whitehouse 2 (TW2) [233] methods most widely used. For the Greulich and Pyle method, a radiograph of the left hand and wrist is compared with the standards of the Brush Foundation Study of skeletal maturation in normal boys and girls [232]. The standards correspond to a cohort of white children, so its applicability to other racial groups may be less accurate. The TW2 method assigns a score to each one of the epiphyses. It is more accurate but also more time consuming. BA estimation has technical difficulties due to inter- and intraobserver variations as well as ethnic and gender differences among children.

## Prediction of Adult Height

The growth potential of an individual must be evaluated according to the parents' and siblings' heights, as genetic influences play a crucial role in determining the adult height. An approximation of the ultimate adult height is obtained by calculating the midparental height. For girls, midparental height is (mother's height + father's height—13 cm)/2 and for boys (mother's height + father's height + 13 cm)/2. The child's target height is the midparental height ± 2 S.D. (10 cm or 4 in) [234]. When the growth pattern deviates from the parental target height, an underlying pathology must be ruled out.

Four methods to predict adult height are available: (1) Bayley-Pinneau is based on current stature, chronological age, and BA obtained by the Greulich and Pyle method [235]. This method probably underpredicts growth potential [236]. (2) The TW2 method considers current height, chronologic age, TW2 assessment of BA, midparental stature, and pubertal status [233]. (3) The Roche-Wainer-Thissen method requires recumbent length, weight, chronological age, midparental stature, and Greulich and Pyle BA assessment [237]. (4) The Khamis-Roche algorithm (KR) directly calculates predicted adult height from a linear combination of child's height and weight, together with midparental height. Sex- and age-specific coefficients for both sexes are provided [238]. However, there is wide variation in predicted adult heights using height prediction algorithms, and different methods are useful under certain circumstances, with accuracy varying according to subjects' age, gender, and BA [239]. In addition, predictions of adult height may be of limited value in patients with underlying pathology.

## MR Imaging

Magnetic resonance imaging (MRI) of the brain is a sensitive and specific indicator of hypopituitarism: A high proportion of children with IGHD with normal or small pituitary glands showed normalization of GH secretion at the completion

of GH treatment, whereas GHD was permanent in all patients with congenital anatomical abnormalities, such as pituitary hypoplasia, pituitary stalk agenesis, and posterior pituitary ectopia [211]. Structural abnormalities are more common in patients with CPHD or panhypopituitarism (93%) and in those with severe GH deficiency compared to those with isolated GH deficiency (80%) [240]. Mass lesions such as suprasellar tumors or thickening of the pituitary stalk due to infiltrative disorders such as histiocytosis may be found in patients with acquired GHD.

## GH Therapy

There is wide variability in the dose of rhGH used to treat GHD. Traditionally, rhGH dosage has been based on weight, and consensus guidelines recommend doses of 25–50 μg/kg/day given 6–7 days per week in children with the consideration of doses up to 100 μg/kg/day during puberty [203, 241]. High-dose therapy during puberty has been shown to increase near-adult height modestly without apparent adverse effects or increased rate of skeletal maturation [242]. There is great variability in response to rhGH therapy.

In order to decrease variability and improve adult height outcomes, two strategies have evolved to help refine rhGH dosing. The first strategy employs prediction models which calculate expected growth velocity based on baseline parameters [243]. These prediction models are derived from large pharmaceutical company GH registries and provide important insights into GH responsiveness. Peak GH levels during stimulation testing, age at onset of rhGH therapy, and height deficit from midparental target height have been found to be the most significant predictors of first-year growth velocity [244]. This indicates that individuals with more severe GHD, younger age at therapy start, and greater genetic potential will have the greatest response to therapy. Growth velocity in subsequent years is highly dependent on growth response in the prior year. One study has shown that using individualized rhGH doses based on a prediction model decreased variability in response without compromising efficacy [97].

The second strategy for refining rhGH dosing involves using IGF-I levels to target therapy. One study showed that targeting higher IGF-I levels leads to an increase in height gain without apparent adverse effects [245]. With this strategy, there is still a range of responses which depend on the individual patient's GH sensitivity.

Regardless of strategy used to select a dose for initiation of rhGH therapy, one must assess response to therapy and make further decisions about dose adjustments or discontinuation of therapy. Typically, response is assessed after a year of therapy, and the most important parameters are height velocity and change in height standard deviation score (SDS). Height velocity varies by age and gender, while change in height SDS intrinsically corrects for these factors [246, 247]. In patients with severe GHD defined as a peak GH level <5 ng/mL on stimulation testing, a change in height SDS less than 0.4 in the first year of therapy is a poor response, while in those with less severe GHD, the corresponding value is 0.3 [247]. A suboptimal response may be indicative of an incorrect diagnosis of GH deficiency, lack of compliance, improper preparation and/or administration, associated hypothyroidism, concurrent chronic disease, complete osseous maturation, and, rarely, anti-GH antibodies. Development of antibodies to exogenous GH has been reported in 10–30% of recipients of rhGH. This finding is more common in children lacking the *GH* gene. However, the presence of GH antibodies does not usually attenuate the hormonal effect, as growth failure has been reported in less than 0.1% [248]. Additionally, one can compare actual growth response to predicted growth response based on the aforementioned growth prediction models. As rhGH dose is included in the models, a poor actual versus predicted response indicates either decreased growth hormone sensitivity or noncompliance [247]. Finally, there is mounting evidence that underlying genetic variants in the GH-R influence response to therapy [249], but this area requires further research.

There have been attempts to further increase height gains in individuals with GHD who have a low predicted adult height through the use of gonadotropin-releasing hormone analogs to

suppress puberty. The data on this topic is conflicting, and recent consensus guidelines state that this practice cannot be suggested [250].

Monitoring of IGF-I and IGFBP-3 levels has gained wide acceptance to assess safety and compliance; however, their serum levels do not always correlate with the obtained increment in growth velocity. Although recommended by some [251], regular monitoring of the BA in children under GH therapy is questionable. Interobserver differences in bone age interpretation and erratic changes over time in osseous maturation make the estimation of adult height inaccurate. Similarly, predictions of adult height may be artifactually overestimated, as GH may accelerate the bone maturation in advance to any radiographic evidence [252].

## Side Effects

*Diabetes and insulin resistance*: Despite the concerns of diabetes mellitus (DM) developing in patients under rhGH therapy due to its anti-insulin effect, a higher incidence of type I insulin-dependent diabetes mellitus (IDDM) in children and adults has not been reported [253]. Type II DM has been reported by some at a higher incidence in children receiving GH; however, others found no increased incidence of type 2 DM in rhGH-treated patients with a normal BMI [253]. Nevertheless, a high BMI is a risk factor for developing diabetes in GHD patients, and rhGH therapy may potentially accelerate the development of diabetes in predisposed patients [254].

*Leukemia*: Concerns regarding the development of de novo leukemia arose after a cluster of leukemia in patients under rhGH therapy was reported in Japan in 1988 [255]. A subsequent study, however, which looked at 32,000 rhGH recipients did not find significantly higher incidence compared to the general population [256]. Initially, three cases of leukemia in the United States were reported in 59,736 patient-years of follow-up, which was not significantly higher when matched by US age, race, and gender, yet three additional cases found in an extended follow-up suggested an increased minimum rate of leukemia (2.26 cases expected, $p = 0.028$). Five of these six subjects, however, had antecedent cranial tumors and four had received radiotherapy. More recently, the National Cooperative Growth Study (NCGS) published data to help address concerns about de novo leukemia in recipients without risk factors and report the safety issue has not been confirmed [257]. In patients with idiopathic GHD, there was no increase in leukemia [258].

*Recurrence of central nervous system tumors*: GH and IGF-1, which both have anabolic and mitogenic effects, have been suggested to cause proliferation of normal and malignant cells. Therefore, several possible mechanisms regarding rhGH's potential role in tumor growth have been investigated [259]. Initial data from the Kabi International Growth Study (KIGS) [260] and the NCGS [261] did not support an increased risk of brain tumor recurrence. Follow-up data by the NCGS in 2010, which essentially comprises 20 years of GH therapy and 192,345 patient-years, continued to report no increase in new malignancies or recurrences of CNS tumors in rhGH-treated patients without risk factors [257]. The development of second neoplasms (SN) in children treated with rhGH therapy, however, does appear to be increased especially in those with prior exposure to radiation [257]. Ergun-Longmire et al. reported that cancer survivors treated with rhGH appeared to have an increased risk of developing SN compared to survivors not treated (relative risk 2.15), although the elevation of risk appeared to diminish with increasing length of follow-up [262].

*Skin cancer*: The statistics of the NCGS have not shown a higher incidence of melanocyte nevi or skin cancer in individuals treated with rhGH [263].

*Benign intracranial hypertension*: This neurological complication has been described in patients receiving rhGH but with a low incidence. A prospective study collecting data on 3,332 children in Australia and New Zealand found a low incidence of 1.2 cases per 1,000 patients [264]. More recently, data from the KIGS further demonstrate the incidence is lower than previously

reported [265]. Nevertheless, an ophthalmologic evaluation is mandatory in rhGH recipients in the event of persistent headaches, nausea, visual symptoms, and dizziness.

*Slipped capital femoral epiphysis* (*SCFE*): The NCGS reported that children with GH deficiency were significantly more likely to develop SCFE while on rhGH (91.0/100,000 patient-years) than the general population. Typically, these children were older, heavier, and grew more slowly during the first year of GH treatment than those who did not [266]. Children with idiopathic short stature on GH treatment did not show an increased incidence (9.5/100,000 patient-years). More recently, data from the KIGS analysis demonstrated that the incidence of SCFE was comparable and even lower than previously reported, except for those in the congenital GH-deficient and Turner syndrome groups [265]. SCFE, however, can be associated with not only obesity but also untreated endocrine conditions (e.g., hypothyroidism) that affect growth, trauma, and radiation exposure. Although the incidence of SCFE in all databases appears to remain greater than for the general population, it is difficult to assess the risk of SCFE in the general population because of several variables (age, sex, race, geography) [257, 265].

## Conclusions

Congenital anomalies or anything that damages the hypothalamus, pituitary stalk, or pituitary gland can result in GHD. It is now recognized that there are molecular defects at multiple levels of the GH axis that can also result in GHD. Diagnosis of GHD, however, remains problematic. Once it is diagnosed, rhGH therapy is an effective treatment.

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