Pediatric Endocrinology

A Practical Clinical Guide

Third Edition

Sally Radovick
Madhusmita Misra
Editors

Springer

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This textbook is dedicated to Margaret MacGillivray (Aug. 30, 1930–Sept. 17, 2016), for her vision in editing the first edition and with thanks for asking me to join her. I knew Margaret as a colleague, a mentor, and a friend. For those of us that were lucky enough to know her, she will be remembered as an outstanding clinician, investigator, mentor, and leader. Her passion for pediatric endocrinology, her compassion for others, and her upbeat spirit made her not only a most respected colleague but also a deeply valued friend.

Margaret was a towering figure in pediatric endocrinology making groundbreaking contributions to it. A true professional and role model, Margaret contributed to almost every aspect of pediatric endocrinology: thyroid disease, disorders of growth and puberty, and diabetes. In the mid-1960s, she published a seminal study on growth hormone secretion, defining for the first time short stature in children commonly seen with delayed puberty. She was a true physician scientist, investigating the factors that regulate growth hormone in these affected children. Her legacy to our field will be the pioneering use of growth hormone treatment for children with dwarfism. With this impact, Margaret is alive today and for generations to come.

I met Dr. MacGillivray in 1995 when she was president of the Pediatric Endocrine Society. I believe she never sought to be a leader, but became one naturally through her brilliance, compassion, patience, and selflessness. Her presidential address to the society was inspirational as I was beginning my career. I got to know Margaret well as a member of a prestigious grant review panel and little did I know that she had recommended my membership. Her guidance was critical as I was beginning to develop my academic reputation. In her gentle well-meaning, but somewhat blunt, way, she asked me if I had considered the insecurity associated with my academic position and whether the benefits were sufficient (which I had only cursorily considered). My salary was being funded entirely by NIH grants, which were subject to the vagaries of federal funding; I had 2 children and was married to a physician scientist. It was this discussion that changed my career course. She asked me to consider "replacing her" (imagine that) in Buffalo as she was thinking about stepping down as division director. Unfortunately, this did not work out, but her "reality check" stayed with me as I made my future career decisions. Twenty years later, I followed in her footsteps and was elected president of the Pediatric Endocrine Society.

On several occasions, we discussed the need for a pediatric endocrinology textbook focused on the knowledge required by clinicians that was comprehensive, organized,

and relevant. Agreeing in principal, she gained the support of Humana Press and asked me to co-edit the book with her. This was again an example of her mentorship, allowing me to share her academic stature. Her main goal, reflected in the preface, was to encourage the senior author of each chapter to include "a junior coauthor" as an opportunity to learn, to be mentored, and to give the next generation recognition in the field. With this third edition, we continue her tradition of a junior colleague as coauthor.

My relationship with Margaret has taught me most about the importance of mentorship. She taught mentorship by example and never demanded of her mentees what she would not expect of herself. She brilliantly mentored a generation of doctors with her characteristic compassion, grace, wisdom, and clever sense of humor. She was and still is an inspiration to women who pursue a career in medicine – very seldom looking backward to difficulties she had to endure as a woman, rather looking always forward. Some women would be very angry and bitter, but she always looked back on that as a challenge, and she overcame it. There were no role models or mentors at the time. She broke the glass ceiling and became the role model. Although she was dedicated to her roles as professor, clinician, and researcher, she was passionate about her role as wife, mother, and grandmother.

She taught me that hard work, determination, refusal to give up when the going gets rough, and, above all, sticking to one's ideals make for a successful career and a contented life. Margaret was a star. She didn't just shine; she blazed.

In this spirit, I welcome Madhu Misra as a co-editor of the third edition. Dr. Misra is the Fritz Bradley Talbot and Nathan Bill Talbot professor of pediatrics, Harvard Medical School, and division chief of pediatric endocrinology at the Massachusetts General Hospital. Her clinical interests include disorders of the pituitary gland and bone. Her research interests include the neuroendocrine and bone consequence of conditions that span the nutritional spectrum from anorexia nervosa to exercise-induced amenorrhea to obesity and conditions such as autism spectrum disorder and major depressive disorders.

Additionally, Dr. Misra is known for her successful mentorship of the next generation of pediatric endocrinologists and her service to the field as exemplified by her distinguished service to the Pediatric Endocrine Society.

Sally Radovick, MD

Preface

We welcome you to the third edition of *Pediatric Endocrinology: A Practical Clinical Guide*. The aim of this edition remains similar to the previous: to provide practical detailed and concise guidelines for the clinical management of pediatric endocrine diseases and disorders. Thus, the audience includes pediatric endocrinologists, pediatricians, and primary care physicians who provide medical care for children and adolescents.

The scope of the text continues to include the most common and the most challenging diseases and disorders seen by both primary care physicians and pediatric endocrinologists. We have encouraged the involvement of a junior coauthor to give recognition to our young investigators in the field. We believe we have assembled a state-of-the-art, comprehensive text on the practice of pediatric endocrinology.

Although the main focus of this text is on diagnosis and treatment, each author has included a brief discussion on pathophysiology and molecular mechanisms. The chapters have been organized in such a way as to present the following elements in synchrony: (1) a table of contents and key points; (2) an introductory discussion with background information; (3) a brief overview of recent progress on the mechanism involved; (4) a discussion of the etiology and clinical features that characterize each condition; (5) a delineation of the criteria used to establish a diagnosis; (6) a therapy section which comprehensively reviews the options available and the risks and benefits of each approach corroborated by clinical trial and outcome data, includes information on the long-term safety and efficacy of the treatment modality, and cites guidelines when available; (7) where relevant, a discussion of psychosocial and quality-of-life issues; and (8) finally a new section in this edition which includes related case studies and relevant questions.

Due to the dynamic clinical practice of pediatric endocrinology, extensive revisions and significant changes have been made to reflect current knowledge and practice. We have added chapters and expanded chapter content on care of gender nonconforming/transgender youth, diagnosis and management of osteoporosis, mineralocorticoid disorders and hypertension, and delayed puberty and hypogonadism.

We are most thankful for the generous contributions of our author colleagues. We hope you find the textbook helpful, and we are, of course, open to your comments.

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Growth Disorders

Childhood Growth Hormone Deficiency and Hypopituitarism

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1

Key Points

- 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.
- Hypopituitarism due to mutations in genes involved in pituitary development may be associated with other developmental anomalies.
- The diagnosis of GH deficiency should be made on the basis of physical findings and the integration of auxologic, biochemical, and radiographic data.
- Potential adverse effects of GH therapy include benign intracranial hypertension, slipped capital femoral epiphysis, and progression of scoliosis.

1.1 Introduction and Background Information

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

The anterior pituitary, which comprises 80% of the pituitary, consists of three parts: the pars distalis (pars anterior or anterior lobe), the pars intermedia (intermediate lobe), and the pars tuberalis (pars infundibularis or pars proximalis). In humans, the pars distalis is the largest portion of the anterior pituitary and where most of the anterior pituitary hormones are produced [3]. The intermediate lobe is poorly developed in humans with only a tiny remnant in adults, although more obvious in the fetus and in pregnant women [4]. The upward extension of the pars distalis onto the pituitary stalk forms the pars tuberalis, which may contain a small number of gonadotropin-producing cells [3].

Peptide hormones 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 and synthesis of several hormones [5]. The anterior pituitary 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 (also known as 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 GH physiology is important and follows below.

Growth hormone is a single-chain α-helical non-glycosylated polypeptide. The majority (90%) of circulating GH is a 22-kDA form consisting of 191 amino acids and two intramolecular disulfide bonds [3, 7]. There is also a 20-kDa variant form, which arises from alternative splicing during the processing of human GH pre-mRNA [8, 9]. 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 (GHR) [10].

The *GH1* gene encodes for GH and is part of a 50-kb cluster of five genes located on human chromosome 17q22–24: *GH1*, *chorionic somatomammotropin* (*CS*)*-like* (*L*), *CS-A*, *GH-2*, and *CS-B* [11]. The CS-L translated protein appears nonfunctional, while CS-A and CS-B encode human chorionic somatomammotropin (hCS), also known as human placental lactogen (hPL). 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 GHR. Interestingly, hCS does not appear necessary for fetal or extrauterine growth, nor does it appear essential for maintenance of pregnancy or lactation [12]. The *GH-2* gene product, which is

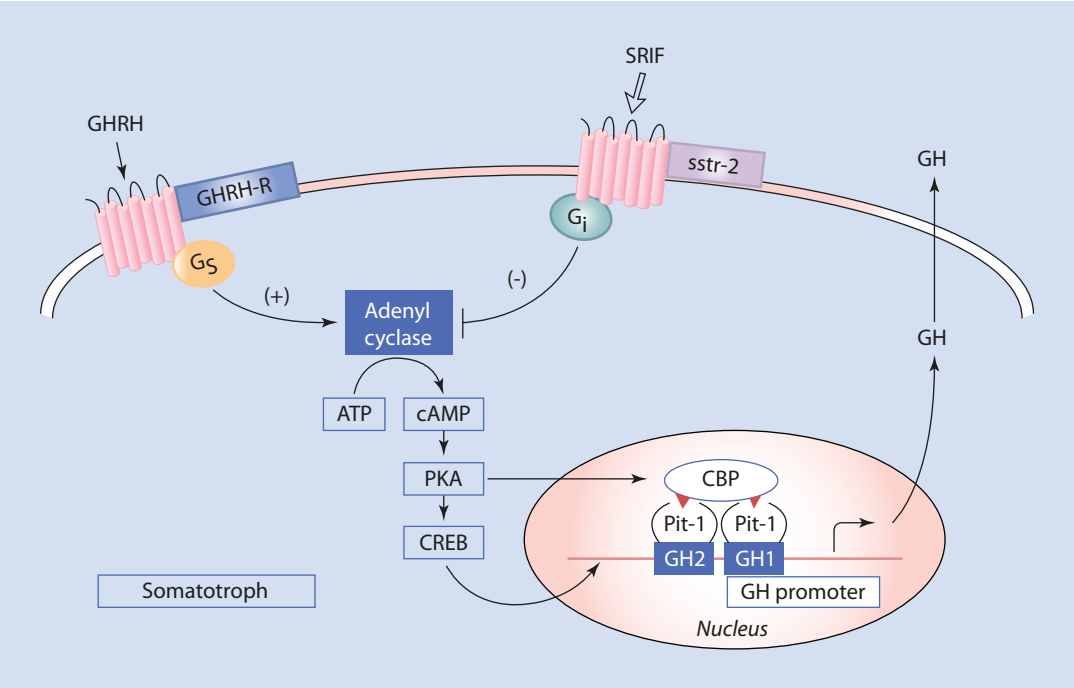

Fig. 1.1 GH secretion. Simplified model of growth hormone (GH) gene activation. GH synthesis and release from somatotrophs are regulated by growth hormone-releasing hormone (GHRH) stimulation and somatostatin (SRIF) inhibition. GHRH activation of its Gs-protein-coupled receptor leads to an increase in 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 POU1F1 and CREB-binding protein (CBP). SRIF activation of its Gi-coupled protein leads to a decrease in cAMP and a reduction in calcium influx

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 [13, 14].

GH is secreted in a pulsatile manner due to the opposing actions 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 (GHRHR), which is a G-protein-coupled receptor with seven-transmembrane-spanning domains with three extracellular and three cytoplasmic loops [15]. Activation of the GHRHR results in an increase in cyclic adenosine monophosphate (cAMP) and intracellular calcium, leading to the activation of protein kinase A (PKA) [16, 17]. PKA phosphorylates and activates cAMP response element-binding protein (CREB), which binds to cAMP response elements in the *GH* promoter to enhance *GH-1* gene transcription [18, 19]. 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) [20] (Fig. 1.1).

SRIF, a 14-amino-acid neuropeptide, negatively regulates GH release primarily via the 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] (Fig. 1.1).

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 may be secondary to the effect of gonadal steroids on GHRH [25–27]. Although GH production continues throughout life, the levels decline in the elderly [28, 29].

There are multiple other factors that affect GH secretion. Thyroid hormone regulates GH secretion at the level of the hypothalamus and pituitary, and hypothyroidism is associated with a decrease in GH secretion [30]. Adiposity (in particular visceral fat) is associated with decreased GH secretion [31], while undernutrition leads to oversecretion of GH but low IGF-I levels indicating GH resistance [32].

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 [33, 34]. These peptides can initiate and amplify pulsatile GH release; however, this is accomplished via the GHS receptor (GHS-R), which is distinct from the GHRHR [34]. 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 [35].

An endogenous ligand for the GHS-R, ghrelin, stimulates GH release in a dose-related manner, as well as potentiates GHRH-dependent secretion of GH [36, 37]. 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 [38]. Several studies have demonstrated that ghrelin has a wide range of effects, including acting as a physiological mediator of feeding [39, 40]. Thus, it is difficult to separate the direct effects of ghrelin from those related to GH secretion.

Approximately 50% of circulating GH is bound to GH-binding protein (GHBP). GHBP is produced in multiple tissues, with the liver being the 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 GHR levels and activity. In rodents, GHBP appears to be synthesized de novo from alternative splicing of *GHR* mRNA. In humans, rabbits, and others, it is shed from membrane-bound GHR by proteolytic cleavage [10, 41].

The GHR is a 620-amino-acid protein that belongs to the cytokine family of receptors [42]. It consists of a large extracellular domain, a single transmembrane helix, and an intracellular domain [43]. The highest level of *GHR* expression is in the liver, followed by the muscle, fat, kidney, and heart. GH binds to a homodimer complex of the GHR in order to activate its intracellular signaling pathways. The subunits of the GHR are constitutively dimerized in an unbound or inactive state [44, 45]. 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, which allows downstream kinase activation by phosphorylation of Janus kinase 2 (Jak2) [45]. Subsequently, the Jak2 molecule induces tyrosine phosphorylation on the intracellular portion of the GHR, which then provides docking sites for intermediary signal transducers and activators of transcription (STAT) proteins [46–48]. After phosphorylation, STATs dimerize and move to the nucleus, where they activate gene transcription [49, 50] (Fig. 1.2).

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 [51]. IGF-I, which is a basic 70-amino-acid peptide, is produced under the direction of GH predominantly in the liver [52]. It plays an important role in both embryonic and postnatal growth. Both systemic and local IGF-I have been shown to stimulate longitudinal bone growth [53–57].

Human fetal serum IGF-I levels, which are approximately 30–50% of adult levels, have been positively correlated with gestational age [58, 59]. The levels of IGF-I gradually increase during childhood and peak during pubertal development, achieving two to three times the normal adult values [60, 61]. IGF-I production is also augmented by the rise in gonadal steroids, which contribute to the pubertal growth spurt. After adolescence, serum IGF-I concentrations decline gradually with age [59, 62]. IGFs circulate within the plasma complexed to

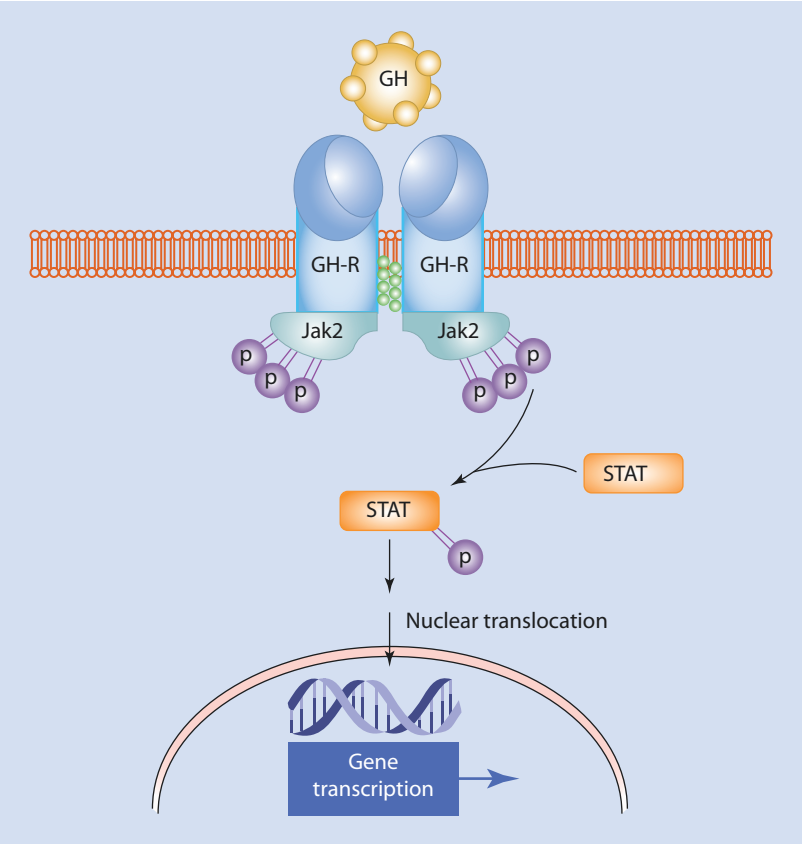

Fig. 1.2 GH action. Schematic model of growth hormone receptor (GHR) binding and signaling. A single GH molecule binds asymmetrically to the extracellular domain of two receptor molecules, causing a conformational change. This leads to interaction of the GHR with Janus kinase (Jak2) and tyrosine phosphorylation of both Jak2 and GHR, 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

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 [59, 63]. Six distinct IGFBPs have been cloned and sequenced [64, 65]. IGFBP-3, which is GH dependent, is the major IGFBP in human serum and transports over 90% of the circulating IGF-I [3].

The IGF-I receptor (IGF-IR), which is structurally related to the insulin receptor, is a heterotetramer comprised of two-membrane-spanning α-subunits and two intracellular β-subunits [66, 67]. The subunits contain binding sites for IGF-I, are linked by disulfide bonds, and 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, 68].

1.2 Etiology of Growth Hormone Deficiency

1.2.1 Congenital Forms of GH Deficiency (▸ Box 1.1)

The incidence of congenital isolated GHD (IGHD) has been reported as between 1:4000 and 1:10,000 live births [69, 70]. Congenital cranial malformations, including holoprosencephaly, septo-optic dysplasia (SOD) spectrum, and midline craniocerebral or midfacial abnormalities, can be associated with anomalies of the pituitary gland, including pituitary hypoplasia or aplasia [6]. Clinically, they may be associated with pituitary hormone deficiencies at birth or with the risk for developing future hormone deficiencies. Although these conditions often have no identifiable etiology, ongoing advances in understanding

Box 1.1 Congenital Forms of Hypopituitarism. Congenital Causes of or Associations with Growth Hormone Deficiency

- 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)
  - GHRH receptor
  - Ventral diencephalon factors
    - FGF8
    - GLI2
  - Pituitary developmental factors
    - Pituitary primordium factors
      - HESX1
      - OTX2
      - PITX2
      - LHX3
      - LHX4
      - SOX3
      - SOX2
    - Pituitary transcription factors
      - PROP1
      - POU1F1
  - GH-1
  - Types Ia, Ib, II, and III
  - Multiple GH family gene deletions
  - Bioinactive GH
  - GH receptor
  - IGF-I
  - IGF-I receptor
  - Stat5b

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.

1.2.1.1 GHRH Receptor Mutations

Inactivating mutations reported in the GHRHR are often classified as a type of IGHD. The little mouse (*lit*/*lit*), which demonstrates dwarfism and decreased number of somatotrophs, has a recessively inherited missense mutation in the extracellular domain of the gene for *Ghrhr* [71–73]. In addition to GHD, these mice exhibit postnatal growth failure and delayed pubertal maturation [73]. The first human mutation identified was a nonsense mutation that introduced a stop codon at position 72 (E72X) in two cousins who presented clinically with the typical phenotype of severe GHD [74]. Subsequently, a nonsense mutation was found in codon 50 in "Dwarfism of Sindh" in Pakistan [75]. Since then, more than 30 nonsense, missense, and splice site mutations in the *GHRH* gene and deletions and regulatory mutations of the POU1F1-binding sites in the GHRHR promotor have been identified [76].

1.2.1.2 Pituitary Developmental Factor Mutations

The 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. Mutations in genes involved in pituitary development may be associated with other developmental anomalies (Table 1.1).

Developmental Factors

Gli2 Gli transcription factors mediate Sonic hedgehog (Shh) signaling, which controls cell fate specification and proliferation in multiple tissues. Gli2/Shh signaling controls the expression of genes in the ventral diencephalon that are necessary for the early patterning of Rathke's pouch, as well as proliferation of pituitary progenitors [80]. Mice deficient in Gli2 have early forebrain, spinal cord, skeleton, and ventral diencephalon defects with variable pituitary loss. Pituitary cell types develop, but corticotrophs, somatotrophs, and lactotrophs do not proliferate [81]. Mutations in GLI2 have been found in patients with GH deficiency alone or with one or more other anterior pituitary deficiencies with and without holoprosencephaly and in patients with holoprosencephaly with and without pituitary hormone deficiencies. When pituitary hormone deficiencies are present, the GLI2 protein is usually truncated; when pituitary hormone deficiencies are absent, there is usually a missense mutation. The anterior pituitary may be absent or hypoplastic, and there may or may not be an ectopic posterior pituitary (EPP). Polydactyly is often an associated finding [82].

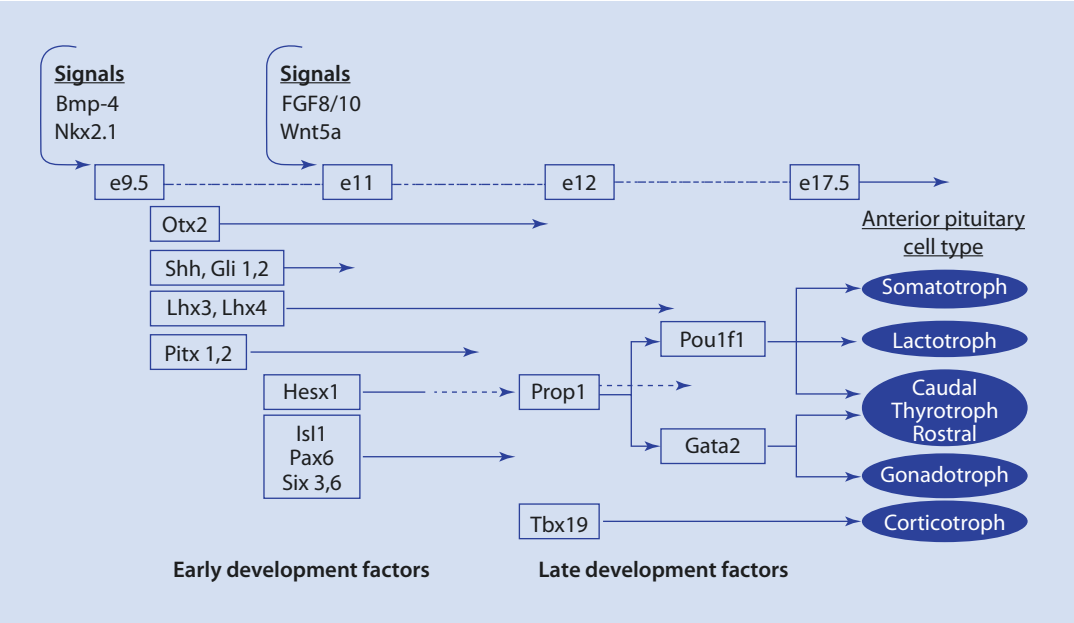

Fig. 1.3 Anterior pituitary development. The development of the mature pituitary gland initiates with the contact of the oral ectoderm with the neural ectoderm followed by a cascade of events consisting of both signaling molecules and transcription factors expressed in a specific temporal and spatial 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 morphogenetic protein 4 (Bmp-4) and NK2 Homeobox 1 (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 [77–79]

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, although no target genes for Hesx1 have been identified [83, 84]. Hesx1 null mutant mice demonstrate abnormalities in the corpus callosum, anterior and hippocampal commissures, and septum pellucidum, a phenotype similar to the defects seen in humans with SOD [83]. The initial report of a human HESX1 mutation was in two siblings with agenesis of the corpus callosum, optic nerve hypoplasia, and panhypopituitarism who 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 [83]. Subsequently, autosomal recessive and dominant HESX1 mutations have been found in association with SOD (although a rare cause of SOD) or with combined pituitary hormone deficiency (CPHD) [85].

Several investigators have screened patients with a wide spectrum of congenital hypopituitarism for mutations in *HESX1*. Thomas et al., for example, evaluated 228 patients: 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 [86]. In another study, 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 [87]. As the described mutations in *HESX1*

Table 1.1 Developmental abnormalities seen in association with hypopituitarism due to mutations in genes involved in pituitary development

Gene	Associated findings
GLI2	Holoprosencephaly Midline defects Polydactyly
FGF8	Holoprosencephaly
HESX1	Optic nerve hypoplasia Absent septum pellucidum and corpus callosum
OTX2	Micro- or anophthalmia
LHX3	Cervical spine/vertebral anomalies Deafness Hyperextensible joints
LHX4	Hypoplastic corpus callosum Chiari syndrome
SOX2	Micro- or anophthalmia Esophageal atresia Sensorineural hearing loss
SOX3	Absent corpus callosum Craniofacial abnormalities

present with variable phenotypes, it has been suggested the hormone abnormalities may be affected by modifier genes or environmental factors [88].

Otx2 *Otx* genes 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* [89]. Otx2 is expressed in the ventral diencephalon, where it interacts with Hesx1, and in Rathke's pouch. Homozygous inactivation of Otx2 in mice leads to extreme brain defects, while heterozygous inactivation results in eye abnormalities, commonly pituitary hypoplasia, and sometimes holoprosencephaly. Heterozygous mutations of the *OTX2* gene, which have been implicated in severe ocular malformations such as anophthalmia, have also been reported in patients with hypopituitarism ranging from GH deficiency to multiple pituitary hormone deficiencies [90–93]. There are variable findings of hypoplastic pituitary, EPP, and Chiari syndrome [94–98].

Pitx2 (Ptx2) Pitx2 is a paired-like homeodomain transcription factor closely related to the mammalian *Otx* genes [89]. Pitx2 null mice showed embryonic lethality; however, a hypomorphic allele model of Pitx2 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 [99–101].

RIEG is the human homologue of Pitx2, 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 [102]. One group of investigators described mutations in six out of ten families with autosomal dominant Rieger syndrome [103, 104]. Five of the six mutations reported were in the homeobox region, and several showed loss of DNA-binding capacity.

Lhx3 (Lim-3, P-Lim) and Lhx4 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. Lhx3 expression persists in the adult pituitary, suggesting a maintenance function in one or more of the anterior pituitary cell types [105]. 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 [105, 106].

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 [107–109]. Among 366 studied patients with idiopathic GHD or CPHD, only 7 patients from 4 families were found to have LHX3 mutations, suggesting *LHX3* mutations are a rare cause of CPHD [109]. A compound heterozygous mutation of LHX3 was described that leads to a short protein inducing a dominant negative effect (from a paternally derived change) and a protein with impaired transactivational ability (from a maternally derived change) [110]. As with other described *LHX3* mutations, the patient presented with pituitary hormone deficiencies, in addition to deafness and limited neck rotation.

Lhx4 is a closely related transcription factor to Lhx3. Heterozygous sporadic and familial LHX4 mutations have been reported. Pituitary hormone

deficiencies range from IGHD to panhypopituitarism, and the pituitary may be hypoplastic with or without an EPP. Some patients also have corpus callosum hypoplasia or Chiari syndrome with pointed cerebellar tonsils [111].

Other transcription factors In addition to the more commonly cited factors, several other mutated developmental factors have been reported to cause CPHD [111]. Sox2, for example, has roles both in pituitary development and in the stem cell compartment [112]. Patients with reported Sox2 mutations presented with phenotypes including hormone deficiencies (primarily isolated gonadotroph deficiency), pituitary hypoplasia, and eye abnormalities [113, 114]. Another interesting development has been the association of pituitary hormone deficiencies with mutations in the gonadotroph genes prokineticin receptor 2 (*PROKR2*), fibroblast growth factor 8 *(FGF8)*, and FGF receptor 1 (*FGFR1*), which have been traditionally reported in patients with isolated hypogonadotropic hypogonadism [115].

Pituitary-Specific Transcription Factors

Prop1 Prop1 is a paired-like homeodomain transcription factor with expression restricted to the anterior pituitary during development [2, 116]. During pituitary development, Prop1 acts as a repressor in downregulating Hesx1 and as an activator of Pou1f1 [77]. Recent evidence suggests that Prop1 may play a more central role in pituitary stem cell differentiation than previously recognized [117].

A considerable variation in clinical phenotypes of patients with PROP1 mutations has been demonstrated, even in patients bearing identical genotypes [116, 118, 119]. Several reports have shown that the hormone deficiencies may be variable and dynamic; some patients may develop hypogonadotropic hypogonadism despite the progression into spontaneous puberty or cortisol deficiency over time [116, 120–122]. Interestingly, some patients present with pituitary hyperplasia prior to developing hypoplasia, which is speculated to be due to pituitary progenitors accumulating in the intermediate lobe rather than differentiating into more mature cell types [123].

At least 25 heterozygous or compound heterozygous human mutations have been described [111]. The most common is a recurring homozygous autosomal recessive mutation of PROP1, delA301, and 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. It has been found in nonconsanguineous patients from at least eight different countries [124–126].

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 [127, 128]. 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 [128].

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 [129–132]. At least 28 different mutations have been described, with 23 demonstrating autosomal recessive inheritance and 5 demonstrating dominant inheritance [78]. 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 [130, 132–140]. 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 thus another mechanism responsible for CPHD [141]. 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 [78, 142].

1.2.1.3 Isolated GHD

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 [143–146]. In addition to *GH1* gene abnormalities, a recent report, in siblings with IGHD, described two homozygous variants in the proximal GH1 promoter within a highly conserved region and predicted binding sites [147]. Patients with IGHD type 1A frequently develop antibodies to exogenous GH therapy, which is attributed to the lack of immune tolerance because of prenatal GHD [148, 149]. Some patients may eventually become insensitive to GH replacement therapy demonstrating a decreased clinical response; subsequently, recombinant IGF-I 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 [144, 150, 151]. 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 frameshift within exon 5. These changes ultimately affected the stability and biological activity of the mutant GH protein [152]. Several other deletions or frameshift mutations have been described by others [153–155].

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 [151, 152, 156–160].

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 [161, 162].

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-I 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 [163]. In another patient, an aspartic acid to lysine mutation at codon 112 was identified and suggested to prevent appropriate GHR dimerization [164].

There are also patients with the phenotype of growth hormone insensitivity who do not demonstrate mutations of the GHR gene, but have identified mutations in downstream GHR signaling molecules. Homozygous mutations in STAT5B, a major GH-dependent mediator of IGF-I gene transcription, have been identified as a cause of GH insensitivity [165, 166]. The first mutation characterized was a point mutation resulting in a marked decrease in phosphorylation of tyrosine [166], a critical step in the pathway to STAT activation of *IGF-I* gene transcription; while the second characterized mutation was an insertion in exon 10, leading to early protein termination [165, 167, 168]. In addition to growth retardation, both patients had evidence of immune dysfunction presumably because STAT5B is involved in downstream signaling for multiple cytokines.

1.2.1.4 GHR Mutations

Laron dwarfism is an autosomal recessive disorder characterized by clinical features of severe GH deficiency along with low IGF-I levels but with normal to high levels of GH after provocative testing [169]. Several deletions and point mutations of several GHR exons have been described [170–179]. Many of these mutations affect the extracellular domain and, therefore, lead to absent or decreased levels of GHBP [180]. Recombinant IGF-I therapy has been demonstrated to effectively treat these patients [181, 182]. 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 *GHR* gene [178].

1.2.1.5 IGF-I and IGF-IR Mutations

A patient noted to have a homozygous partial IGF-I gene deletion with undetectable levels of IGF-I 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 [183]. Subsequently, a few other cases of IGF-I mutations have been described.

Studies with African Pygmies demonstrate normal levels of GH but decreased IGF-I levels and unresponsiveness to exogenous GH. Although

IGF-I deficiency has been hypothesized, Bowcock et al. found no differences in restriction fragment length polymorphisms in the IGF-I gene in Pygmy versus non-Pygmy black Africans [184]. Furthermore, Pygmy T cell lines show IGF-I resistance at the receptor level with secondary GH resistance [185, 186]. In subsequent studies, it was demonstrated that adult Pygmies demonstrate a reduction in both GH gene expression (1.8-fold) and GHR gene expression (8-fold). This decrease of the GHR expression in Pygmies was associated with reduced serum levels of IGF-I and GHBP [187].

Abnormalities in the IGF-IR gene have also been reported and are often associated with intrauterine growth retardation (IUGR). Several heterozygous mutations of the IGF-IR gene, as well as an association with deletions in chromosome 15q, have been reported in patients with growth retardation [188–193]. 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-I levels were found to be either normal or high, whether at baseline or after provocative testing.

Other patients are suspected to have IGF-I resistance, as they have elevated GH levels and elevated IGF-I levels [194–196]. In one patient, cultured fibroblasts had a 50% reduction in IGF-I binding capacity [194]. Another patient had a markedly diminished ability of IGF-I to stimulate fibroblast α-aminoisobutyric acid uptake compared to control subjects [195]. Their birth lengths, which were less than the fifth percentile, suggest the importance of IGF-I in fetal growth.

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

1.2.2 Acquired Forms of GH Deficiency (► Box 1.2)

Hypopituitarism can be caused by anything that damages the hypothalamus, pituitary stalk, or pituitary gland. Head trauma can injure the pituitary stalk and infundibulum and lead to the development of transient and permanent diabetes insipidus, as well as other hormonal deficiencies [197, 198]. There are a number of reports suggesting an association between hypopituitarism and a complicated perinatal course, especially breech delivery [199, 200]. 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].

Infiltrative conditions can also disrupt the pituitary stalk. Diabetes insipidus can be the first manifestation of germ cell tumors, Langerhans cell histiocytosis [201–203] or sarcoidosis [204]. Lymphocytic hypophysitis, usually in adult women in late pregnancy or in the postpartum period, can result in hypopituitarism [205].

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 [206, 207].

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 [208]. Treatment of brain tumors or acute lymphoblastic leukemia (ALL) with cranial

Box 1.2 Acquired Forms of Hypopituitarism. Etiologies of Acquired Growth Hormone Deficiency

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

irradiation may also result in GHD. Lower radiation doses preserve pharmacologic response of GH to stimulation, but spontaneous GH secretion may be lost [209]. Discordancy between failure to provoke an adequate GH response to insulin-induced hypoglycemia and normal response to exogenous GHRH stimulation suggest that the hypothalamus is more vulnerable than the anterior pituitary [210]. 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 postulated 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 the time of increased GH demand [211].

The higher the radiation dose, the more likely and the earlier GHD will occur after treatment [212, 213]. 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 [212]. Higher doses also increase the likelihood of the development of other anterior pituitary hormone deficiencies [213]. Cranial radiation can also be associated with precocious puberty, leading to premature epiphyseal fusion [198], and spinal irradiation can lead to skeletal impaired spinal growth [214], both of which will further compromise adult height.

1.3 Clinical Presentation of Growth Hormone Deficiency

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 prenatal environment wane [215]. They generally have normal birth weights and lengths slightly below average [216]. The height percentile of a child with GH deficiency will progressively decline, and typically the bone age will be delayed. They develop increased peri-abdominal fat [217] and decreased muscle mass and may also have delayed dentition, thin hair, poor nail growth, and a high-pitched voice [215]. 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 [215].

1.4 Diagnostic Evaluation 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. The diagnosis of GHD should be based on the integration of auxological, biochemical, and radiographic criteria.

GHD should be considered in children with short stature, defined as a height more than 3 SD below the population mean or height more than 2 SD below the population mean with a growth velocity more than 1 SD below the mean, and in children with a very low growth velocity (more than 2 SD below mean) irrespective of current height. In considering who should undergo evaluation for GHD, it is important to first exclude other causes of growth failure and then assess the patients for clinical features that can coexist with GHD. These features include hypoglycemia, prolonged jaundice, microphallus, traumatic delivery in the neonate, and craniofacial midline abnormalities. Additionally, history of other pituitary hormone deficiencies, cranial radiation, and central nervous system infection, as well as family history of GHD, should be ascertained [218]. 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-I levels [219] and low peak GH levels after stimulation tests [220]. Nonetheless, the majority of patients with GHD will present with short stature without any of these other features.

1.4.1 IGF-I and IGFBP-3

GH induces the expression of IGF-I in the liver and cartilage. The use of age and puberty-corrected IGF-I levels has become a major tool in the diagnosis of GHD [221]. Because of little diurnal variation, their quantification in random