Disorders of Growth and Development: Diagnosis and Treatment

2.1 Clinical Rounds

1. Who does need to be evaluated for short stature?
   Evaluation for short stature is indicated in a child whose:
   
   • Height >3SD below the mean for age and gender
   Or
   • Height <−2SD with a height velocity ≤−1SD over a period of 12 months
   Or
   • Height velocity SDS <−2SD over a period of 12 months
   Or
   • Predicted adult height >1.5SD below the target height
   Or
   • Growth curve crosses downward by ≥1 centile curve in the growth chart over a period of 12 months

2. Why is height SDS of −3 recommended for the evaluation of short stature?
   Although a height >2SD below the mean for age and gender is used to define short stature, evaluation of short children based on this criteria yields organic etiology only in 14% of these children. However, when a height SD ≤−3 is considered for the evaluation of short stature, the proportion of children with organic causes increases to 58%. Nevertheless, children with height between −2SD and −3SD need careful monitoring for growth velocity, and if they show faltering, they need further evaluation.

3. Does a single measurement of height suggest growth failure?
   A single measurement of height does not suggest growth failure, unless the child is extremely short (≤−3SD). The serial measurement of height determined
over a period of time, preferably for 6–12 months, helps to calculate the height velocity. Short stature when compounded with decreased height velocity suggests growth failure and demands further evaluation.

4. **Who does need an urgent evaluation for GHD?**

The auxological criteria which demands urgent evaluation for GHD include severe short stature (height <−3SD) or height <−2SD with height velocity <−1SD over 1 year or height velocity <−2SD over 1 year. Any neonate with symptoms and signs of GHD/MPHD or any child with sellar–suprasellar mass should be urgently evaluated for GHD, irrespective of auxological criteria. In addition, any short child with signs and symptoms of an intracranial lesion should also be urgently evaluated.

5. **What are the investigations required for evaluation of a short child?**

A detailed history and physical examination usually provides clues to the differential diagnosis of short stature and guide further investigations. The minimum investigations to be done in a short child are complete blood count, creatinine, urine analysis, bicarbonate, calcium, phosphorous, alkaline phosphatase, SGOT, SGPT, albumin, TSH, T₄, and celiac serology (IgA tTG). Karyotype should be done in all girls with unexplained short stature and/or delayed puberty. X-ray for bone age predicts child’s growth potential and also may give clues to certain differential diagnosis (rickets/dysplasia). These investigations are mandatory before proceeding for GH-IGF1 dynamics.

6. **What is the “ternary complex” in GH-IGF axis?**

The “ternary complex” comprises of IGF1, IGFBP3, and acid labile subunit (ALS) in equimolar ratio. Serum IGF1 and ALS are synthesized in hepatocytes, while IGFBP3 in the Kupffer cells of the liver. All the components of ternary complex including IGF1, IGFBP3, and ALS are GH-dependent. The ternary complex prolongs the half-life of IGF1 (from 10 min to 12–15 h) and regulates the bioavailability of IGF1 to target sites. Therefore, patients with mutation of ALS gene have reduced serum levels of IGF1 and IGFBP3. However, growth impairment in these children is modest due to preserved local IGF1 generation at the growth plate.

7. **What are the merits and demerits of serum IGF1 in the diagnosis of growth hormone deficiency?**

Serum IGF1 is a measure of integrated growth hormone secretion. In addition, the circulating levels of IGF1 are stable with minimal diurnal variation. Therefore, estimation of serum IGF1 is a useful tool for the assessment of GH–IGF1 axis. It has a sensitivity and specificity of 70% each, for the diagnosis of GHD in older children, but the sensitivity is lesser (50%) in younger children (<6 years) because
of higher degree of overlap between normal and abnormal values in this age group. Therefore, IGF1 is considered as a good screening test for the diagnosis of GHD in older children. However, serum IGF1 levels are influenced by age and nutritional status, and its generation is dependent on optimal levels of insulin, thyroid hormones, and gonadal steroids. Further, IGF1 assays are technically challenging as it requires separation of IGF1 from IGFBP3.

8. **What is the utility of serum IGFBP3 in the diagnosis of growth hormone deficiency?**

Serum IGFBP3 is GH-dependent and is a measure of integrated GH secretion. Its circulating levels are stable with no diurnal variation. It is not influenced by age, nutritional status, or other endocrine factors. Further, assays for IGFBP3 are relatively technically less demanding. Therefore, IGFBP3 serves as a useful measure for the assessment of GH–IGF1 axis and has a sensitivity and specificity of 60% and 80–90%, respectively, for the diagnosis of GHD. It is preferred in the diagnosis of GHD in younger children (<6 years), because of its higher discriminatory value as compared to IGF1. Limited data is available regarding the use of combination of IGF1 and IGFBP3 for the diagnosis of GHD in children.

9. **What is the utility of random GH estimation in the diagnosis of GHD?**

Growth hormone secretion is pulsatile with four to six pulses at night during non-rapid eye movement (NREM) sleep and three to four pulses during daytime in the postabsorptive phase. Therefore, random estimation of GH may not be useful for the diagnosis of GHD. However, random GH sampling is useful in the evaluation of patients with suspected neonatal GHD and growth hormone insensitivity. A random serum GH value <7 ng/ml in the first week of life (along with clinical signs or symptoms) suggest the diagnosis of neonatal GHD. Random GH >5 ng/ml in the presence of low IGF1 is diagnostic of growth hormone insensitivity.

10. **What is the role of integrated GH sampling in the evaluation of GHD?**

There are conflicting reports regarding the utility of integrated GH sampling for the evaluation of GHD. Although it is a measure of 24h spontaneous GH secretion, it is seldom used in clinical practice as it is labor intensive, expensive, and has poor sensitivity.

11. **What is neurosecretory dwarfism?**

Some children with short stature have low serum IGF1 despite normal GH response to provocative stimulation tests. However, on 24h integrated GH sampling, these children have abnormalities in GH secretory profile including
decreased pulse amplitude or frequency (or both) or reduced mean 24h GH concentration. These children are termed as “neurosecretory dwarfs” and are thought to have functional defects in the neuroendocrine regulation of GH secretion. However, the term neurosecretory dwarfism is obsolete and these children are classified under the category of idiopathic short stature (ISS). Children with neurosecretory dysfunction show excellent response to rhGH therapy.

12. What is the need for GH dynamic tests in the evaluation of GHD?

Although auxology is the best index for the assessment of GHD, biochemical assessment of GH–IGF1 axis is required for the confirmation of the same. Random GH estimation has limited value in the diagnosis of GHD as GH secretion is pulsatile, and the GH levels can range from <0.1 ng/ml during the nadir to >30 ng/ml during the peak, even in normal individuals. Serum IGF1 is a good screening test; however, there is a great degree of overlap between the levels found in normal children and those with GHD (i.e., low sensitivity). In addition, serum IGF1 is influenced by many factors other than GH. Because of these limitations, GH dynamic tests are employed for the evaluation of GHD.

13. When should a short child be evaluated for GHD?

Since GHD is a rare cause of short stature, evaluation of GH–IGF1 axis is recommended only after careful exclusion of common causes of growth failure including chronic systemic diseases (e.g., celiac disease, renal tubular acidosis), hypothyroidism, rickets, Turner’s syndrome, pseudohypoparathyroidism, and skeletal dysplasias.

14. What are the various GH dynamic tests employed for the evaluation of GHD?

Dynamic tests for the evaluation of GHD can be physiological or pharmacological. The physiological stimuli used are exercise and sleep, whereas pharmacological stimuli include insulin-induced hypoglycemia, clonidine, glucagon, L-dopa, arginine, GHRH, and combined GHRH–arginine.

15. What are the prerequisites for GH dynamic testing?

GH secretion is regulated by various factors which include diet, sleep, exercise, thyroid hormones, cortisol, and gonadal steroids. Dietary constituents like amino acids stimulate GH secretion, while glucose and free fatty acids inhibit GH secretion. Therefore, GH dynamic tests are recommended to be performed in the fasting state. Thyroxine has a permissive role in GH–IGF1 secretion;
therefore, euthyroidism should be ensured prior to GH dynamic tests. In addition, gonadal steroids also influence GH–IGF1 secretion; hence, priming with estrogen/testosterone should be considered in children above 8 years of age having Tanner stage \( \leq 2 \). GH dynamic tests should not be performed in children receiving >15 mg/m\(^2\)/day of hydrocortisone or its equivalents, as this may lead to more false-positive results.

16. *What is the rationale of “priming” prior to GH dynamic testing?*

Gonadal steroids potentiate GH secretion and this results in GH–IGF1 surge during puberty. Hence, priming with gonadal steroids is required to optimize GH response to provocative stimuli in children of peripubertal age. However, there are controversies regarding the need for priming, the age at which priming should be done and which agent should be used for priming. Priming with gonadal steroids is suggested in children above 8 years of age having Tanner stage \( \leq 2 \).

17. *How to prime with gonadal steroids before GH dynamic testing?*

The various protocols for priming are summarized in the table given below.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Protocol</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated equine estrogen</td>
<td>5 mg PO in the previous night and in the morning of test</td>
<td>Less preferred</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>0.1 mg PO for 3 days, prior to test</td>
<td>Can be used in both boys and girls</td>
</tr>
<tr>
<td>Estradiol valerate</td>
<td>2 mg PO for 3 days (&gt;20 Kg), prior to test</td>
<td>Can be used in both boys and girls</td>
</tr>
<tr>
<td></td>
<td>1 mg PO for 3 days (&lt;20 Kg), prior to test</td>
<td></td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>100 mg IM injection 3 days prior to test</td>
<td>Can be used only in boys</td>
</tr>
</tbody>
</table>

18. *What are the mechanisms of growth hormone release in response to GH dynamic tests?*

GH secretion is a consequence of interplay between growth hormone-releasing hormone (GHRH) and somatostatin at the level of hypothalamus and pituitary. GHRH stimulates the synthesis and release of GH, while somatostatin exerts an inhibitory effect on GH secretion. Alterations in the somatostatin tone determine the pulsatility of GH secretion. The mechanism of action of various GH secretagogues is summarized in the table given below.
### Tests and Mediators

<table>
<thead>
<tr>
<th>Tests</th>
<th>Mediator</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-induced hypoglycemia</td>
<td>Low plasma glucose (glucoreceptors at hypothalamus)</td>
<td>↓ Somatostatin via cholinergic receptors&lt;br&gt;↑ GHRH via α₂-adrenergic receptors</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Norepinephrine</td>
<td>↑ GHRH via α₂-adrenergic receptors</td>
</tr>
<tr>
<td>Glucagon stimulation test</td>
<td>Glucagon</td>
<td>↑ GHRH via α₂-adrenergic receptors&lt;br&gt;↓ Somatostatin via cholinergic receptors</td>
</tr>
<tr>
<td>Glucagon stimulation test</td>
<td>Glucagon</td>
<td>Direct stimulatory effect of peptidyl fragments on somatotropes</td>
</tr>
<tr>
<td>l-Dopa</td>
<td>Dopamine</td>
<td>↑ GHRH via α₂-adrenergic receptors&lt;br&gt;↓ Somatostatin via cholinergic receptors</td>
</tr>
<tr>
<td>Arginine</td>
<td>Arginine</td>
<td>↓ Somatostatin</td>
</tr>
<tr>
<td>GHRH</td>
<td>GHRH</td>
<td>Direct effect</td>
</tr>
<tr>
<td>Ghrelin and analogues</td>
<td>Ghrelin</td>
<td>Increases GHRH release&lt;br&gt;Potentiates the effect of GHRH</td>
</tr>
</tbody>
</table>

### 19. What are the merits and demerits of different GH dynamic tests?

The merits and demerits of different GH dynamic tests are summarized in the table given below.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Merits</th>
<th>Demerits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-induced hypoglycemia (IIH)</td>
<td>Gold standard&lt;br&gt;Assess multiple pituitary hormones (GH, ACTH, prolactin, and ADH)</td>
<td>Risk of severe hypoglycemia which can cause seizure and arrhythmia</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Reproducible&lt;br&gt;Oral route</td>
<td>Less effective in older children&lt;br&gt;Causes sedation and hypotension</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Preferred in children&lt;br&gt;Also assess ACTH reserve</td>
<td>Causes nausea and vomiting</td>
</tr>
<tr>
<td>l-Dopa</td>
<td>Oral route</td>
<td>Causes sedation&lt;br&gt;Less potent</td>
</tr>
<tr>
<td>Arginine–GHRH</td>
<td>Most potent&lt;br&gt;Safe&lt;br&gt;Reproducible</td>
<td>Expensive&lt;br&gt;Limited availability&lt;br&gt;Falsely negative in those with hypothalamic causes of GHD</td>
</tr>
<tr>
<td>Ghrelin and analogues</td>
<td>Potent</td>
<td>Limited data</td>
</tr>
</tbody>
</table>
20. **Which is the preferred GH dynamic test?**

Insulin-induced hypoglycemia is considered as the gold standard for the diagnosis of GHD. However, the test is associated with adverse events; hence, clonidine and glucagon stimulation tests are commonly performed in clinical practice. Considering the merits and demerits of different GH dynamic tests, arginine–GHRH seems to be an alternative to these tests; however, cost and limited availability precludes its routine use in clinical practice.

21. **Why is there a need for two dynamic tests in the diagnosis of GHD?**

At least two GH dynamic tests are required for the confirmation of the diagnosis of GHD due to low specificity of these tests. Both the tests should be abnormal to make a definitive diagnosis of GHD. However, a single dynamic test is sufficient to diagnose GHD in those with structural pituitary defects or multiple pituitary hormone deficiencies.

22. **How to define GH deficiency after GH dynamic tests?**

For the diagnosis of childhood GHD, a peak serum GH level <10 ng/ml after provocative stimuli is considered as subnormal, whereas a cutoff <7 ng/ml is considered as severe GHD. In spite of the differences in relative potency and mechanism of action, the stimulated levels of GH differ modestly between the different dynamic tests. Hence, the same GH cutoffs are used to define GHD while using various tests. However, when using GHRH–arginine a cutoff ≤19 ng/ml is suggested because of its high potency.

23. **What are the limitations of GH dynamic tests in childhood GHD?**

GH dynamic tests are nonphysiological and have poor specificity and reproducibility. These tests assess pituitary GH reserve but do not provide information regarding pulsatility of GH secretion and bioactivity. Hence, a normal peak GH response to a dynamic test may not necessarily translate into optimal linear growth. In addition, the cutoffs for the diagnosis of GHD are arbitrary and do not take into account the effect of age and BMI on GH dynamics. There is also controversy regarding priming with sex steroids. Lastly, the risks associated with GH dynamic tests like hypoglycemia, seizure, and hypotension limit their use in clinical practice.

24. **What is the importance of CT/MR imaging in the evaluation of children with GHD?**

All patients with documented GHD should be subjected to MR imaging of the sellar region to exclude the possibility of sellar–suprasellar mass lesions, structural defects of pituitary gland and stalk or midline defects. In addition, CT head may be required to detect calcification in patients with craniopharyngioma (Figs. 2.1, 2.2, and 2.3).
Fig. 2.1 (a) Sagittal CEMRI and (b) sagittal T2W MR image showing a predominantly cystic suprasellar mass lesion (red arrow) suggestive of craniopharyngioma.

Fig. 2.2 Coronal CEMRI demonstrates a hypoplastic pituitary gland (red arrow) in a child with panhypopituitarism. Also note cavum septum pellucidum (arrow head).
What is MRI “tetrad” associated with GHD/MPHD?

The MRI tetrad includes small sella, hypoplastic/absent anterior pituitary, redundant/absent pituitary stalk, and ectopic/absent posterior pituitary bright spot. The presence of these structural defects in a short child is highly predictive of multiple pituitary hormone deficiency; hence, only a single GH dynamic test is required to establish the diagnosis of GHD in these patients. The presence of these abnormalities is also suggestive of irreversible GHD; therefore, GH dynamic tests may not be required during transition to adulthood in these patients (Fig. 2.4).
26. What is septo-optic dysplasia?

Septo-optic dysplasia (SOD) includes midline defects of brain (absence of septum pellucidum, corpus callosum agenesis), optic nerve dysplasia, and pituitary hypoplasia. Two out of these three abnormalities are required for the diagnosis of SOD. Familial forms of SOD are caused by HESX1 transcription factor defect and are associated with multiple pituitary hormone deficiency including vasopressin (Fig. 2.5).

Fig. 2.4 (a) A 20-year-old male with short stature and delayed puberty due to multiple pituitary hormone deficiency. (b) Sagittal CEMRI showing small pituitary (red arrow), redundant stalk, and ectopic posterior pituitary bright spot (arrow head) suggestive of pituitary transcription factor defect.
Fig. 2.5  (a) A 21-year-old boy with panhypopituitarism and septo-optic dysplasia. (b) Fundus examination showing temporal pallor of left optic disc. (c) Electretinogram depicting absence of a and b wave in the left eye. (d) Visual evoked responses revealed absence of waveforms in the left eye. (e) CEMRI sella demonstrating classical tetrad (ectopic posterior pituitary bright spot, red arrow) of pituitary transcription factor defect. (f) Coronal MR image depicting left optic nerve hypoplasia as compared to right optic nerve (red arrow)
Fig. 2.5 (continued)
27. **What is waxing and waning pituitary?**

Alterations in the size of the pituitary gland in children with congenital GH or multiple pituitary hormone deficiency due to PROP1 transcription factor defects have been described during the course of disease. “Waxing” is probably due to physiological compensatory hyperplasia of the residual pituitary cells due to increase in the expression of transcription factors like HESX1 which is normally repressed by PROP1 or due to hypertrophy of the intermediate lobe and “waning” is due to ongoing pituitary damage and fibrosis.

28. **How to treat a child with growth hormone deficiency?**

A child with documented growth hormone deficiency should be treated with rhGH in a dose of 0.18–0.35 mg/Kg/week (1 mg = 3 IU). The rhGH is administered subcutaneously, daily between 8 and 9 pm to mimic the physiology of GH secretion. Optimal response to GH requires adequate nutrition and regular physical activity. In addition, regular surveillance for the development of thyroid hormone and cortisol deficiency is required to optimize the response to rhGH therapy.

29. **What are the predictors of response to rhGH therapy?**

The predictors of response to rhGH therapy include optimal doses, daily administration, initiation of therapy at an early age, severity of GH deficiency, pretreatment growth velocity, and genetic potential of an individual. In addition, individuals with GH receptor polymorphism (GHRd3) have been shown to respond better to rhGH therapy. However, children with previous spinal irradiation exhibit suboptimal response to rhGH therapy.

30. **How to adjust the doses of rhGH in a child with GHD?**

Optimal growth response is the best index to assess the adequacy of rhGH therapy in a child with GHD. The dose of rhGH should be periodically adjusted on the basis of body weight. If the growth response is not adequate, dose of rhGH should be increased to 0.35 mg/Kg/week after ensuring compliance to therapy and exclusion of hypothyroidism. If the growth response is suboptimal even after adequate doses of rhGH, serum IGF1 should be measured and if low, a possibility of resistance to GH should be considered. In addition, estimation of serum IGF1 is recommended at periodic intervals to ensure compliance and safety. However, serum IGF1 level alone should not be used to increase the dose of rhGH therapy as IGF-based dosing schedules are associated with higher requirement of rhGH (about 2.5 times) as compared to weight-based regimens. The higher doses of rhGH are associated with more adverse events and do not translate into increased linear growth. Persistently (>2 years) high serum IGF1 (>2SD) should be avoided as it may be associated with an increased risk of malignancy. It has been shown that increasing the doses of rhGH during puberty (up to 0.7 mg/Kg/week) results in increased final adult height by approximately 4.6 cm (Fig. 2.6).
31. How to monitor a child on rhGH therapy?

After initiation of GH therapy, auxological parameters including height, weight, body proportions, and waist circumference should be monitored at three monthly intervals. Height velocity should be monitored six monthly and bone age annually. In addition, children should be evaluated for the development of hypothyroidism, hypocortisolism, and dysglycemia. Serum IGF1 should be estimated after 3 months of initiation of therapy and yearly, thereafter. Serum IGF1 should not exceed the normal reference range for age and gender (>2SD), as it may be associated with adverse events. The child also needs to be under regular surveillance for the development of side effects like edema, gynecomastia, papilloedema (pseudotumor cerebri), slipped capital femoral epiphysis, pancreatitis, and worsening of preexisting scoliosis (Figs. 2.7 and 2.8).
Fig. 2.7 (a, b)
Development of scoliosis in a child after rhGH therapy

Fig. 2.8 (a, b)
Development of gynecomastia in an 18-year-old boy with multiple pituitary hormone deficiency after rhGH therapy. Patient did not receive prior testosterone therapy
32. What is the expected growth response to rhGH therapy in children with GHD?
Treatment with rhGH results in a brisk growth response of 10–12 cm in the first year and 7–9 cm in the second and third years, followed by 5 cm/year thereafter. The height SDS should increase by at least 0.25 SDS in the first year of treatment. Suboptimal response to rhGH therapy should raise a suspicion of poor compliance, malnutrition, coexisting celiac disease, and hypothyroidism. After exclusion of these causes, further titration of rhGH doses should be based on body weight, growth velocity, and pubertal development.

33. Why is there a decline in growth velocity with the continued use of rhGH?
Initiation of rhGH therapy is associated with a rapid increase in growth velocity in the first year, followed by progressive decline in efficacy over the next few years. This phenomenon was initially thought to be associated with the development of anti-GH antibodies; however, the antibody titers were not sufficient to interfere with the action of GH. Increased chondrocyte recruitment and proliferation from the resting zone of epiphyseal growth plate is responsible for catch up growth after the initiation of GH therapy. The subsequent reduction in the efficacy of rhGH over the years is due to the progressive decline in the chondrocyte reserve, and increased “chondrocyte senescence” has been suggested as possible mechanisms.

34. What are the causes of suboptimal response to rhGH therapy?
Besides technical reasons (optimal dose, daily administration, and injection techniques), the important causes of suboptimal response to rhGH therapy include development or unmasking of secondary hypothyroidism, concurrent presence of celiac disease, malnutrition, previous spinal irradiation, and development of anti-GH antibodies particularly in those with GH gene (GH-N) deletion.

35. Why is it necessary to monitor serum $T_4$ in patients on rhGH therapy?
Therapy with rhGH results in increased peripheral conversion of $T_4$ to $T_3$, leading to decrease in $T_4$ and increased $T_3$. These changes usually occur within first 3 months after initiation of therapy and resolves spontaneously by 6–12 months. Some studies have shown a decrease in TSH after rhGH therapy; this may be due to inhibition of thyrotropes as a consequence of increased $T_3$ and augmented somatostatin tone. The development of hypothyroidism is uncommon in majority of patients; however, rhGH therapy may unmask central hypothyroidism in individuals with multiple pituitary hormone deficiency. Hence, it is recommended that thyroid function tests should be performed after 3 months of initiation of rhGH therapy and annually thereafter.
36. **When to induce puberty in children with multiple pituitary hormone deficiency those who are on rhGH therapy?**

In children with multiple pituitary hormone deficiency, those who are on rhGH therapy from childhood, and those who have a normal growth, puberty should be induced with gonadal steroids at a chronological age of 11–12 years in girls and 12–13 years in boys, if there is evidence of gonadotropin deficiency (e.g., micropenis, cryptorchidism). However, in children with multiple pituitary hormone deficiency, who were initiated on rhGH at a later age and have subnormal prepubertal height, puberty should be induced at the age of 13 years in girls and 14 years in boys. Further delaying the induction of puberty may have a negative impact on psychosocial development and bone health. For induction of puberty, gonadal steroids should be initiated at low doses and the doses are progressively increased over a period of 3–4 years. However, prior to initiation of gonadal steroids, a child with MPHD should be optimally replaced with L-thyroxine, as under or over replacement may interfere with growth and puberty. Overtreatment with glucocorticoids should be avoided as it adversely affects growth and puberty. It has been shown that increasing the doses of rhGH during puberty (up to 0.7 mg/Kg/week) results in increased final adult height by approximately 4.6 cm.

37. **What is the role of combination therapy with rhGH and GnRH agonists in children with isolated GHD?**

Delaying the onset of puberty may improve the final adult height in children with short stature at the onset of puberty. Combination therapy with rhGH and GnRH agonists may be considered in children with GHD and having short stature at the onset of puberty. However, studies of combined use of rhGH and GnRH agonists have shown variable results. Hence, the routine use of rhGH and GnRH agonists in children with isolated GHD is not recommended.

38. **When to discontinue rhGH therapy in a short child?**

The primary aim of treatment with rhGH in a short child is to achieve a final adult height as close to the target height as possible. The end points for discontinuation of rhGH therapy include achievement of the target height, decrease in growth velocity to <2 cm/year or closure of epiphysis. However, patients with persistent GHD due to underlying genetic or structural defects and some patients with idiopathic GHD require continuation of rhGH therapy during adulthood.
39. **What are the long-term risks associated with rhGH therapy in children with GHD?**

It has been shown that long-term rhGH therapy in children with GHD is associated with higher risk of mortality and increased risk of neoplasms. In a recent study, Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE), it was demonstrated that rhGH therapy for children with short stature was associated with an increase in all-cause mortality with a standardized mortality ratio (SMR) of 1.33. Patients who received higher doses of rhGH (>50 μg/Kg/day) had an increased incidence of bone tumors, subarachnoid/intracerebral hemorrhage, cardiovascular events, and an increased all-cause mortality with a SMR of 2.94. The risk of second neoplasms (i.e., benign meningioma) is higher in children treated with rhGH who were childhood survivors of primary brain tumors and had exposure to cranial irradiation. However, the risk of tumor recurrence is not increased in children with cranio-pharyngioma, nonfunctional pituitary tumors, medulloblastoma, and germ cell tumors after rhGH therapy.

40. **Is there a need for continuation of rhGH therapy during adulthood?**

Growth hormone is not only required for linear growth but is also essential for the maintenance of normal body composition, cardiovascular health, skeletal integrity, and quality of life. Adult GHD is associated with altered body composition (decreased lean mass and increased fat mass), visceral adiposity, adverse lipid profile (high LDL-C and low HDL-C), insulin resistance, hypertension, increased procoagulant activity, systolic dysfunction, and increased cardiovascular mortality. In addition, GHD is also associated with poor quality of life, low bone mineral density, and increased risk of fracture. Therapy with rhGH results in improvement in body composition, lipid profile, inflammatory markers, bone mineral density, and quality of life. However, rhGH therapy has not been shown to improve cardiovascular mortality in adults with GHD.

41. **Do all children with GHD require reassessment during transition to adulthood?**

Approximately 50% of children with isolated idiopathic GHD do not have persistent disease on retesting during adulthood, whereas 96% of children with multiple pituitary hormone deficiency have persistent GHD. Hence, reassessment of GH–IGF1 axis during transition to adulthood is done on the basis of presence or absence of structural abnormality or multiple pituitary hormone deficiency. An approach to a child with GHD during transition to adulthood is shown in the figure given below (Fig. 2.9).
42. **Who are the children likely to have reversible GHD during transition to adulthood?**

Approximately 50% of children with idiopathic isolated GHD have reversible growth hormone deficiency, as evidenced by normal GH dynamic studies during adulthood. The cause of this reversibility is not well explicated. It may be possibly due to recovery from transient disruption of neuroendocrine alteration in GH–IGF1 axis. Alternatively, reversibility may be due to change in diagnostic cutoffs of GHD for adults.

43. **Who should be tested for adult-onset GHD?**

As idiopathic isolated GHD is rare in adults, only those with a high probability of having GHD are to be tested for adult-onset GHD. Hence, adults with hypothalamic–pituitary disorders, traumatic brain injury, subarachnoid hemorrhage, and those with multiple pituitary hormone deficiency should be screened. In addition, those with history of cranial irradiation and surgery in hypothalamic–pituitary region should also be tested. In adults with organic disease and having MPH (≥3 hormone deficiency), a low IGF1 is highly suggestive of GHD and GH dynamic tests may not be necessary. However, in those with organic disease and having <3 hormone deficiency, serum IGF1 and a single GH dynamic test should be done to establish a diagnosis of GHD. Two GH dynamic tests are recommended before making a diagnosis of idiopathic isolated GHD in adults.
44. What are the GH dynamic tests recommended for the diagnosis of GHD in adults?

Insulin-induced hypoglycemia (IIH) and GHRH–arginine test are the recommended GH dynamic tests for the diagnosis of GHD in adults. However, if IIH is contraindicated (seizure disorder, coronary artery disease) or GHRH–arginine is not available, glucagon stimulation test can be performed. In those with hypothalamic causes of GHD, GHRH test is not preferred as the test is falsely normal in these individuals. The cutoffs to define GHD in adults are summarized in the table given below.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Peak GH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIH</td>
<td>&lt;5.1</td>
</tr>
<tr>
<td>GHRH+arginine</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;25 Kg/m²</td>
<td>&lt;11.5</td>
</tr>
<tr>
<td>BMI 25–30 Kg/m²</td>
<td>&lt;8</td>
</tr>
<tr>
<td>BMI &gt;30 Kg/m²</td>
<td>&lt;4.2</td>
</tr>
<tr>
<td>Glucagon</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

45. Why are cutoffs for the diagnosis of GHD lower in adults?

Serum GH cutoffs are lower for the diagnosis of GHD in adults as there is a progressive decline in function of somatotropes after puberty. In addition, lower levels of GH are required in adults (for metabolic effects) as compared to children (for linear growth).

46. Why is the dose of rhGH lower in adults as compared to children with GHD?

GH secretion is higher in children and adolescents as compared to adults. There is a progressive decline in GH secretion and hepatic sensitivity to GH with advancing age; hence, serum IGF1 levels progressively declines with aging. Therefore, the dose of rhGH (for promoting linear growth) in children is much higher than in adults with GHD (for the improvement in metabolic profile and quality of life). The initiating doses of rhGH are 0.2 mg/day and 0.3 mg/day in adult men and women, respectively, and 0.1 mg/day in older individuals. The doses are increased by 0.1–0.2 mg after 1–2 months to maintain serum IGF1 in the upper normal range.

47. Why is the dose of rhGH in adults IGF1-based rather than weight-based?

As opposed to children where weight-based GH regimens are used, IGF1-based regimens are recommended in adults with GHD. In adults, weight-based GH regimens are associated with higher doses and, hence, more adverse effects like pares-
thesia, joint stiffness, peripheral edema, and arthralgia. Higher doses of rhGH do not translate into any additional benefits in metabolic profile as compared to lower doses. Further, there is also high inter-individual variability in GH absorption kinetics from subcutaneous sites in adults as compared to children which favors IGF1-based regimen and precludes the use of weight-based regimen.

48. *Why are the doses of rhGH higher in women than in men with GHD?*

The circulating levels of GH have been shown to be twofold higher in adult women as compared to men, and this is thought to be due to the direct effects of estrogen on GH secretion. However, the circulating levels of IGF1 are almost similar or rather lower in women during adulthood, which is due to the antagonistic effects of estrogen on GH-mediated IGF1 generation at hepatocytes. Hence, women require higher doses of rhGH for the treatment of GHD. Interestingly, during prepubertal and peripubertal period, serum IGF1 levels are higher in girls as compared to boys, probably due to stimulatory effects of low concentration of estrogen on GH-mediated IGF1 generation.

49. *What are the FDA-approved indications of rhGH therapy besides GHD?*

The FDA-approved indications of rhGH therapy in children with short stature without GHD include Turner syndrome, Noonan syndrome, chronic kidney disease, Prader–Willi syndrome, idiopathic short stature (height $<-2.25$ SD), small for gestational age, and SHOX haploinsufficiency (Leri–Weill syndrome). In addition, rhGH therapy is also approved in patients with AIDS-associated cachexia and short bowel syndrome on total parenteral nutrition.

50. *Is GH dynamics mandatory before initiating rhGH therapy in a short child?*

GH dynamics are mandatory to establish the diagnosis of GHD in a short child. However, in children with short stature due to Turner syndrome, Noonan syndrome, Prader–Willi syndrome, small for gestational age, and chronic kidney disease, GH dynamic tests are not required prior to initiation of rhGH therapy. Recombinant hGH therapy should be initiated in children with these disorders when the child starts faltering on standard growth chart and should be followed up on the same growth chart.

51. *Which growth chart is recommended for children with intrinsic short stature?*

The height of children with intrinsic short stature should be monitored on standard growth chart as well as syndrome-specific growth chart. Monitoring of height of a child on standard growth chart allows the early recognition of growth failure (crossing of one centile curve downward) and timely initiation of
rhGH therapy, if indicated. Further, children who are treated with rhGH should be monitored on standard growth chart. A child who falters on syndrome-specific growth chart should be evaluated for secondary causes of growth failure like hypothyroidism, celiac disease, or coexisting GHD.

52. **What are the causes of GH-sufficient short stature?**

Children with systemic disorders, idiopathic short stature, intrinsic short stature, small for gestational age, and GH insensitivity syndrome are short despite GH sufficiency.

53. **Why is higher dose of rhGH recommended in the treatment of children with non-GHD short stature?**

The dose of rhGH used in children with non-GHD short stature is higher (0.375 mg/Kg/week) as compared to that used in children with GHD (0.3 mg/Kg/week). This is because these disorders are GH-resistant states and need supraphysiological doses for optimal growth.

54. **What is Laron syndrome?**

Laron syndrome is an autosomal recessive disorder, which is a prototype of growth hormone insensitivity syndromes (GHIS). The defects in GHIS include defective GH receptor dimerization or post-receptor signaling events resulting in decreased IGF1 generation (e.g., STAT5b mutation) or defective IGF1 stabilization and rarely mutations in IGF1 gene. The characteristic features of Laron syndrome include severe short stature (−4 to −10SDS), midfacial hypoplasia, blue sclera, delayed motor milestones, and hip dysplasia. Despite severe short stature, birth length and birth weight are usually normal. Biochemically, it is characterized by high/normal GH levels along with low IGF1. Disorders like malnutrition, uncontrolled diabetes, and chronic renal failure can also have a similar biochemical profile. Treatment with recombinant human IGF1 is effective in children with Laron syndrome (Fig. 2.10).
Fig. 2.10  (a) A 14-year-old child with Laron syndrome. (b) Note the typical facial features in the same child.
55. How to diagnose GH insensitivity syndrome?

The presence of low IGF1 along with peak GH >15 ng/ml during GH dynamic test in a short child should raise a suspicion of GHIS. The diagnostic criteria (Savage and Blum) for GHIS include height SDS <−3, basal GH >5 ng/ml, serum IGF1 <50 ng/ml, GH binding with GHBP <10 %, and subnormal response to IGF1 generation test. In this test, rhGH is administered daily for four consecutive days at a dose of 0.033 mg/Kg/d subcutaneously at 2000h and serum IGF1 is estimated at baseline and on day 5 at 0800h. An increment in IGF1 of <15 ng/ml is considered subnormal. Three out of these five criteria are required to make a diagnosis of GHIS. In addition, a low serum basal IGFBP3 (<0.1 centile for age) and an increment in IGFBP3 <0.4 mg/L after IGF1 generation test also supports the diagnosis.

56. Why are the pygmies short?

Pygmies are an aboriginal group of people endemic to Africa and characteristically have severe short stature. The severe growth failure in these individuals was thought to be due to IGF1 receptor mutation or defects in downstream IGF1 signaling pathway. However, the recent studies have demonstrated that they have normal levels of GH, low levels of GHBP, and normal to low levels of IGF1. The exact cause of short stature in these individuals is not known; however, defects in GH receptor, IGF1 gene, and IGF1 receptor are the proposed mechanisms. Treatment with recombinant human GH or IGF1 does not improve height in pygmies.

57. What are the causes of tall stature?

An individual with height two standard deviation (>97th percentile) or more above the mean as compared to children of the same age, gender, and ethnicity is considered to have tall stature. The causes include familial tall stature, acrogigantism, Marfan syndrome, homocystinuria, and XYY syndrome. In addition, individuals with hypogonadotrophic hypogonadism, Klinefelter’s syndrome, estrogen receptor mutations, and aromatase deficiency also have tall stature in adulthood (Fig. 2.11).
Increased GH pulse amplitude and relatively higher IGF1 level have been demonstrated in children with familial tall stature. The treatment modalities for adolescents with familial tall stature include testosterone in boys and estrogen in girls. Bromocriptine and somatostatin analogues have been tried in both sexes with limited success.
Further Readings


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