Disorder of Pituitary Gland and Short Stature

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Introduction

Pituitary Gland (Hypophysis)

- **Pituitary**: Literally means “spit mucus” (Latin + Greek)
- **Hypophysis**: Literally mean “Under growth” (Greek)
- **Currently consider as:**
  - Transporter (Master gland Previously translate neural inputs into hormonal (endocrine) responses in regulating other endocrine glands.
- **Absence leads to:**
  - Cessation of growth
  - Profound disturbances in body metabolism
  - Gonadal, thyroidal, adrenal failure
It consists of mainly two lobes

- Adenohypophysis (Anterior lobe) – Rathk’s pouch
- Neurohypophysis (Post lobe) – hypothalmus
- Intermediate lobe (Rudimentary)
Role of hypothalamic neurohormones in regulating secretion of pituitary hormone

AVP (9aa) → (+) ACTH → Adrenal
CRH (41aa) → (+) FSH, LH → Gonads
GnRH (10aa) → (-) PRL(+), (-) TSH(-) → Breast, Thyroid
D (Dopamine) → (+) TSH(-) → Thyroid
TRH (Tripeptide) → (+) GH (+) → Liver
SS (14aa) → (-) GH (+) → Tissues
GHRH (44aa) → Liver

Corticosteroids
Estrogens, Progesterone
In females
Testosterone
In males
T₄, T₃

Liver
IGF-I
The general plan of hypothalamic–pituitary-target gland axis

Inputs producing circadian rhythm
- SL
- LL

Feed back inhibition

Hypothalamic factor

Stress Other inputs

Tropic hormone

Target gland

Hypothalamus

Hormone
## Pituitary Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Structure</th>
<th>Functions</th>
</tr>
</thead>
</table>
| Oxytocin                   | Polypeptide of 9 amino acids | **Uterine contraction**
|                            |                            | **Milk ejection in lactating females**, responds to suckling reflex and estradiol, lower steroid synthesis in testes |
| Vasopressin (9antidiuretic hormone, ADH) | Polypeptide of 9 amino acids | **Responds to osmoreceptor**
|                            |                            | which senses extracellular [Na+], blood pressure regulation, increase H2O reabsorption from distal tubules in kidney |
## Anterior Pituitary Hormone

<table>
<thead>
<tr>
<th>Hormone (by name or abbreviation)</th>
<th>Amino Acid Components</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanocyte-stimulating hormones (MSH)</td>
<td>$\alpha$ polypeptide = 13 amino acids; $\beta$ polypeptide = 18 amino acids; $\gamma$ polypeptide = 12 amino acids</td>
<td>Pigmentation</td>
</tr>
<tr>
<td>Corticotropin (adrenocorticotropic, ACTH)</td>
<td>Polypeptide = 39 amino acids</td>
<td>Stimulates cells of adrenal gland to increase steroid synthesis and secretion</td>
</tr>
<tr>
<td>Lipotropin (LPH)</td>
<td>$\beta$ polypeptide = 93 amino acids; $\gamma$ polypeptide = 60 amino acids</td>
<td>Increases fatty acid release from adipocytes</td>
</tr>
<tr>
<td>Thyrotropin (thyroid-stimulating hormone, TSH)</td>
<td>2 polypeptide: $\alpha$ is 96 amino acids; $\beta$ is 112</td>
<td>Acts on thyroid follicle cell to stimulate thyroid hormone synthesis</td>
</tr>
<tr>
<td>Growth hormone (GH, or somatotropin)</td>
<td>Protein of 191 amino acids</td>
<td>General anabolic stimulant, increases release of insulin-like growth factor-I (IGF-I), cell growth and bone sulfation</td>
</tr>
</tbody>
</table>
Anterior Pituitary Hormone

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Protein Composition</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin (PRL)</td>
<td>Protein of 197 amino acids</td>
<td>Stimulates differentiation of secretory cells of mammary gland and stimulates milk synthesis</td>
</tr>
<tr>
<td>Luteinizing hormone (LH); human chronic gonadotropin (hCG) is similar and produced in placenta</td>
<td>2 proteins: $\alpha$ is 96 amino acids; $\beta$ is 121</td>
<td>Increases ovarian progesterone synthesis, luteinization; acts on leydig cells of testes to increase testosterone synthesis and release and increase interstitial cell development</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>2 πρωτεϊνσ: $\alpha$ 96 αμίνο αχιδσ; $\beta$ 120</td>
<td>Ovarian follicle development and ovulation, increases estrogen production; acts on Sertoli cells of semeniferous tubule to increase spermatogenesis</td>
</tr>
<tr>
<td>Hormone</td>
<td>Structure</td>
<td>Functions</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Corticotropin-releasing factor (CRF or CRH)</td>
<td>Protein of 41 amino acids</td>
<td>Acts on corticotrope to release ACTH and β-endorphin (lipoprotropin)</td>
</tr>
<tr>
<td>Gonadotropin-releasing factor (GnRF or GnRH)</td>
<td>Polypeptide of 10 amino acids</td>
<td>Acts on gonadotrope to release LH and FSH</td>
</tr>
<tr>
<td></td>
<td>γ polypeptide = 60 amino acids</td>
<td></td>
</tr>
<tr>
<td>Prolacctin – releasing factor (PRF)</td>
<td>This may be TRH</td>
<td>Acts on lactotrope to release prolactin</td>
</tr>
<tr>
<td>Prolactin – releasing inhibiting factor (PIF)</td>
<td>May be derived from GnRH precursor, 56 amino acids</td>
<td>Acts on lactotrope to inhibit prolactin release</td>
</tr>
</tbody>
</table>
## Hypothalamic Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Structure</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone – releasing factor (GRF or GRH)</td>
<td>Protein of 40 and 44 amino acids</td>
<td>Stimulates GH secretion</td>
</tr>
<tr>
<td>Somatostatin (SIF, also called growth hormone – release inhibiting factor, GIF)</td>
<td>Polypeptide of 14 and 28 amino acids</td>
<td>Inhibits GH and TSH secretion</td>
</tr>
<tr>
<td>Thyrotropin – releasing factor (TRH or TRF)</td>
<td>Polypeptide of 3 amino acids: Glutamyl – Histidyl – Proline</td>
<td>Stimulates TSH and prolactin secretion</td>
</tr>
</tbody>
</table>
Anterior Pituitary Hormone Function Testing

<table>
<thead>
<tr>
<th>Random hormone measurements</th>
<th>Provocative Stimulation Test</th>
<th>Target hormone measurement</th>
</tr>
</thead>
</table>
| GH (useless as a random determination except in GH resistance or in pituitary gigantism) | Arginine (a weak stimulus) L-Dopa (useful clinically)  
Insulin induced hypoglycemia (a dangerous but accurate test)  
Clonidine (useful clinically GRH  
12-24 hr interated GH levels (of questionable utility) | IGFI, IGF, BP3 (affected by malnutrition as well as GH deficiency) |
| ACTH (early AM sample useful only if in high normal range) | Cortisol after insulin-induced hypoglycemia (a dangerous test)  
11-Desoxycortisol after metyrapone CRH  
ACTH stimulation test (may differentiate ACTH deficiency from primary adrenal insufficiency) | AM Cortisol  
24 hr urinary free cortisol |
| TSH | TRH | FT4 |
| LH, FSH | GnRH (difficult to interpret in prepubertal subjects) | Testosterone  
Estradiol |
| Prolactin (elevated in hypothalmic disease and decreased in pituitary disease) | TRH | None |
## Diagnostic Evaluation of Hypopituitarism

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Cause</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth failure, hypothyroidism, or both</td>
<td>GH deficiency, TRH/TSH deficiency, or both</td>
<td>Provocative GH tests, free T4, bone age, IGFI, IGF BP3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>GH deficiency, ACTH insufficiency, or both</td>
<td>Provocative GH tests, test of ACTH secretion, IGFI, IGF BP3</td>
</tr>
<tr>
<td>Micropenis, pubertal delay or arrest</td>
<td>Hypogonadotrophic hypogonadism or GH deficiency</td>
<td>Sex steroids (E2, testosterone), basal LH and FSH (analyzed by ultrasensitive assays) or after GnRH, administration, provocative GH tests, IGFI, IGF BP3</td>
</tr>
<tr>
<td>Polyuria, polydipsia</td>
<td>ADH deficiency</td>
<td>Urine analysis (sp. Gr.), serum electrolytes, urine and serum osmolality, water deprivation test</td>
</tr>
</tbody>
</table>
General plan for the diagnostic evaluation of hypothalamic pituitary target gland hypofunction

Clinical history and examination

Thyroid function tests
  Serum testostosterone
  Serum TSH, LH, FSH

Rapid ACTH Stimulation test
  Normal
  Low
  Low or normal
  Elevated
  Primary target gland failure
  Low or normal
  Hypopituitarism

Confirm diagnosis, extent of hypofunction, and level of abnormality
CLINICAL PRESENTATIONS OF PITUITARY AND HYPOTHALAMIC DISEASE

1. Hyperpituitarism: excess secretion of one or more anterior pituitary hormones
2. Mass effects: caused by expansion of pituitary tumors
3. Hypopituitarism: deficient secretion of one or more anterior pituitary hormones, observed when about 75% of normal anterior lobe is destroyed
4. Posterior Pituitary Syndromes
   a. deficient secretion of ADH or inadequate renal response to ADH (diabetes insipidus)
   b. excess secretion of ADH (syndrome of inappropriate ADH = SIADH)
5. Suprasellar Mass Lesions: masses originating outside the pituitary which may produce hyperpituitarism, hypopituitarism, or diabetes insipidus
Disorders of Pituitary Function

- **Hypopituitarism**
  - Central hypoadrenalism, hypogonadism, hypothyroidism or GH deficiency
  - Panhypopituitarism

- **Hypersecretion of Pituitary Hormones**
  - Hyperprolactinemia
  - Acromegaly
  - Cushing’s Disease
PITUITARY TUMOURS CAUSING HYPERPITUITARISM

- Pituitary tumours are often functional
- Order of frequency with which hormone secretion occurs ...
  - Prolactin
  - GH
  - ACTH
  - Gonadotrophins
  - TSH (very rare)
- May present with hypopituitarism, intracranial SOL, visual field defects
GROWTH HORMONE EXCESS ... ACROMEGALY AND GIGANTISM

- Gigantism. The affected person is
  - tall and large in all proportions
  - so weak that s(h)e can hardly stand

- Excessive skeletal growth occurs only in the feet, the hands, the molar eminences, the nose, and the chin, giving rise to acromegaly.
Complications of Acromegaly

**Cardiovascular**
- Ischemic heart disease
- Cardiomyopathy
- Congestive heart failure
- Arrhythmias
- Hypertension

**Respiratory**
- Kyphosis
- Obstructive sleep apnea

**Metabolic**
- Diabetes mellitus/IGT
- Hyperlipidemia

**Neurologic**
- Carpal tunnel syndrome
- Stroke

**Neoplastic**
- Colorectal
- (Breast and prostate - uncertain)

**Musculoskeletal**
- Degenerative arthropathy
- Calcific discopathy, pyrophosphate arthropathy

http://www.endotext.com/neuroendo/neuroendo5e/neuroendoframe5e.htm
Diagnosis of Acromegaly

- Random GH – not useful
- Insulin like growth factor 1 (IGF-1) – best for screening
- Oral glucose GH suppression testing – gold standard to confirm diagnosis
HYPERPROLACTINAEMIA

- Amenorrhea
- Galactorrhea
- Loss of libido
- Infertility

Causes include drugs, prolactinoma, tumours blocking dopaminergic inhibition of prolactin secretion, ectopic secretion.
HYPOPITUITARISM

- Can result from hypothalamic or pituitary disease
- Tumours are most common cause
- GH and gonadotrophins affected before that of ACTH
- May be accompanied by hypofunction of posterior pituitary
CAUSES

1. Tumors and other masses (adenomas most common; metastases to pituitary, cysts, encroaching suprasellar masses)
2. Pituitary surgery or radiation (usually for adenoma)
3. Pituitary apoplexy: sudden hemorrhage into an adenoma
4. Ischemic necrosis of anterior lobe after severe birth-related hemorrhage (Sheehan syndrome)
5. Rathke cleft cyst (compression)
6. Empty sella syndrome
7. Genetic defects: congenital deficiencies of one or more pituitary hormones
8. Inflammatory disorders of anterior lobe
9. Hypothalamic lesions (suspect of both hypopituitarism and diabetes insipidus due to ADH deficiency)
Short Stature

- Short stature is a common paediatric problem
- **Definition**
  - Short stature is defined as length/height below:
    - 3rd percentile for age according to the international standard
    - 5th percentile according to standard
    - 3.5 standard deviation (SD) of mean for age, sex, ethnic group + family
- **Growth failure**: failure to attain expected growth leads to short stature
- **Failure to thrive**: refers to infants and children who fail to gain weight often lose weight they may not be short and are underweight for height + lack of well being
Causes of short stature

Nonendocrine causes

- **Genetic short stature**
- **Constitutional short stature**
- **Intrauterine growth retardation**
- ** Syndromes of short stature**
  - Turner’s syndrome and its variants
  - Noonan’s syndrome (pseudo-turner’s syndrome)
  - Prader willi syndrome
  - Laurence Moon and Bardet-Biedl syndromes
  - Other autosomal abnormalities and dysmorphic syndromes
- **Chronic disease**
  - **Cardiac disorders**
    - Left to right shunt
    - Congestive heart failure
  - **Pulmonary disorders**
    - Cystic fibrosis
    - Asthma
Causes of short stature

- Abnormalities of GH action
  - Ldaron’s dwarfism
  - Pygmies
- Psychosocial dwarfism
- Hypothyroidism
- Glucocorticoid excess (Cushing’s syndrome)
  - Endogenous
  - Exogenous
- Pseudohypoparathyroidism
- Disorders of vitamin D metabolism, Rickets
- Diabetes mellitus
- Diabetes insipidus, untreated
Gonadotropin deficiency

Women
- Amenorrhea
  - Primary or secondary
- Infertility

Men
- Decreased libido
- Decreased beard and body hair
DIABETES INSIPIDUS

- Excessive urination due to kidney’s failure to reabsorb water
- Polyuria with low specific gravity
- Serum osmolality and serum sodium increased (increased concentration ions due to free water loss)
- Compensation: excessive thirst and polydipsia
- Two major mechanisms:
  - **CENTRAL**: lesions affecting hypothalamus-posterior pituitary axis, causing deficient secretion of ADH
  - **NEPHROGENIC**: unresponsiveness of renal tubules to adequate ADH
Diagnosis of DI: water deprivation test followed by response to administered vasopressin

MRI of hypothalamic/pituitary region is useful
Contd...

- Diagnosis of DI: water deprivation test followed by response to administered vasopressin
- MRI of hypothalamic/pituitary region is useful
SIADH

- Excessive circulating ADH, with secondary water retention and hyponatremia
- Serious complication: cerebral edema with neurologic dysfunction; seizures may develop if serum Na < 120 mEq/L (nl 135-145)
- Causes of SIADH:
  - Ectopic secretion by malignant neoplasm, most commonly small cell carcinoma of lung
  - Drugs that increase ADH secretion: some diuretics, cyclophosphamide, vincistine
  - Inflammatory lung disease (eg, tuberculosis, sarcoidosis)
  - CNS trauma, infections: of hypothalamus, posterior pituitary
Thanks

WITH BEST WISHES
CLINICAL FEATURES

- Growth hormone deficiency
  - Children
    - Short stature
  - Adults
    - Non specific
    - Fine wrinkling around the face
    - Improved insulin sensitivity
Contd...

- Corticotropin deficiency
  - Fatigue
  - Decreased appetite
  - Weight loss
  - Decreased pigmentation
  - Abnormal response to stress
    - Hypotension
    - Hyponatremia
    - Fever
  - Hypotension
  - Hyponatremia
  - Fever
Contd...

- Hypothyroidism
  - Fatigue
  - Cold intolerance
  - Puffy skin
  - Absence of goiter

- Diabetes Insipidus
  - Polyuria
  - Polydipsia
Diabetes Insipidus

- Excessive urination due to kidney’s failure to resorb water
- Polyuria with low specific gravity
- Serum osmolality and serum sodium increased (increased concentration ions due to free water loss)
- Compensation: excessive thirst and polydipsia
- Two major mechanisms:
  - **Central**: lesions affecting hypothalamus-posterior pituitary axis, causing deficient secretion of ADH
  - **Nephrogenic**: unresponsiveness of renal tubules to adequate ADH
Causes of short stature

- **Gastrointestinal disorders**
  - Malabsorption (e.g. celiac disease)
  - Disorders of swallowing

- **Hepatic disorders**

- **Hematologic disorders**
  - Sickle cell anemia
  - Thalassaemia

- **Renal disorders**
  - Renal tubular acidosis
  - Chronic uremia

- **Immunologic disorders**
  - Connective tissue disease
  - Juvenile rheumatoid arthritis
  - Chronic infection

- **Central nervous system disorders**

- **Malnutrition**
  - Decreased availability of nutrients
  - Far diets
  - Voluntary dieting
  - Anorexia nervosa
  - Anorexia of cancer chemotherapy
GH as Causes of short stature

Endocrine disorders

- **GH deficiency and variants**
  - **Congenital GH deficiency**
    - With midline defects
    - With other pituitary hormone deficiencies
    - Isolated GH deficiency
    - Pituitary agenesis
  - **Acquired GH deficiency**
    - Hypothalamic pituitary tumors
    - Histiocytosis X
    - Central nervous system infections
    - Head injuries
    - Cranial irradiation
    - CNS nervous system vascular accidents
    - Hydrocephalus
    - Empty sella syndrome
## Hormone Effects on Growth

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Bone Age</th>
<th>Growth Rate</th>
<th>Adult Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen excess</td>
<td>Advanced</td>
<td>Increased</td>
<td>Diminished</td>
</tr>
<tr>
<td>Androgen deficiency</td>
<td>Normal or delayed</td>
<td>Normal or decreased</td>
<td>Increased slightly or normal</td>
</tr>
<tr>
<td>Thyroxine excess</td>
<td>Advanced</td>
<td>Increased</td>
<td>Normal or diminished</td>
</tr>
<tr>
<td>Thyroxine deficiency</td>
<td>Retarded</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>GH excess</td>
<td>Normal or advanced</td>
<td>Increased</td>
<td>Excessive</td>
</tr>
<tr>
<td>GH deficiency</td>
<td>Retarded</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol excess</td>
<td>Retarded</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol deficiency</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
## Initial investigation of short stature

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>Anaemia, malnutrition</td>
</tr>
<tr>
<td>ESR</td>
<td>Chronic inflammatory bowel disease</td>
</tr>
<tr>
<td>Calcium, phosphate, alkaline phosphatase</td>
<td>Malnutrition, hypophosphataemic rickets</td>
</tr>
<tr>
<td>Electrolytes, urea, creatinine</td>
<td>Renal failure, adrenal failure</td>
</tr>
<tr>
<td>Thyroxine, TSH</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>09.00 h or postexercise cortisol</td>
<td>Adrenal failure</td>
</tr>
<tr>
<td>Anti Gliadin antibodies/Antimyosis</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Chromosome analysis</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Renal tract disorder</td>
</tr>
<tr>
<td>Stool</td>
<td>Ova + Cyst</td>
</tr>
</tbody>
</table>
## Optional investigation of short stature – guided by preliminary findings

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
</tr>
<tr>
<td>- Insulin-like growth factor-1 (IGF-1)</td>
<td>GH deficiency</td>
</tr>
<tr>
<td>- IGF – binding protein - 3</td>
<td></td>
</tr>
<tr>
<td><strong>Dynamic hormone tests</strong></td>
<td>GH deficiency</td>
</tr>
<tr>
<td>- Glucagon test, Clonidine test, Arginine test</td>
<td>TSH/thyroxine deficiency</td>
</tr>
<tr>
<td>- TRH test</td>
<td>Gonadotrophin deficiency</td>
</tr>
<tr>
<td>- LHRH test</td>
<td>ACTH/cortisol deficiency</td>
</tr>
<tr>
<td>- Tetracosactrin test</td>
<td></td>
</tr>
<tr>
<td>- ACTH measurement</td>
<td></td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>- Osmolality (second sample after overnight fluid restriction)</td>
<td>GH deficiency</td>
</tr>
<tr>
<td>- GH in overnight collection</td>
<td></td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
</tr>
<tr>
<td>- Pituitary area imaging (MRI better than CT scan)</td>
<td>Congenital or acquired structural disorder</td>
</tr>
<tr>
<td>- Ovarian and uterine ultrasound</td>
<td>Pubertal assessment, gonadal dysgenesis</td>
</tr>
<tr>
<td>- Skeletal survey</td>
<td>Definition of skeletal dysplasia</td>
</tr>
</tbody>
</table>
Growth Hormone deficiency

- **Definition**
  - Growth hormone (GH) deficiency is a lack of growth hormone synthesis, release, or effect

- **Causes**
  - **Idiopathic** (the most common form)
  - **Congenital**
    - Congenital absence of the pituitary (empty sella syndrome)
    - Deletion of the GH gene in familial isolated GH deficiency
    - Familial panhypopituitarism
    - GH receptor defect (Laron syndrome)
    - Post – GH receptor defect
    - Often associated with other midline defects: cleft lip, cleft palate, septo optic dysplasia, holoprosencephaly
Hormone deficiency

**Acquired**
- Trauma: perinatal insult, birth trauma, surgical resection of pituitary gland, surgical damage to pituitary stalk, child abuse
- Infection: viral encephalitis, bacterial or fungal infection, tuberculosis
- Vascular: pituitary infarction, pituitary aneurysm
- Pituitary or hypothalamic irradiation
- Chemotherapy
- Tumors: craniopharyngioma, glioma, pinealoma, primitive neuroectodermal tumor (PNET; medulloblastoma)
- Histiocytosis involving the pituitary gland or sella turcica
- Sarcoidosis
- Psychosocial dwarfism
Hormone deficiency

- **Pathophysiology**
  - Lacking GH decreases levels of insulin like growth factor I (IGF-1) which acts on cartilage to stimulate linear growth

- **Genetics**
  - Spontaneous
  - Autosomal recessive
  - Autosomal dominant
  - X-linked forms
Hormone deficiency

- Epidemiology (Age Related)
  - Incidence in the United States is 1 per 4,000
  - Males are more commonly diagnosed than females
  - Two peak ages of diagnosis:
    - Less than 1 year of age, usually because of associated hypoglycemia
    - After 4 years of age, usually because of poor linear growth
Hormone deficiency

- Complications
  - Short stature
  - Lack of self-esteem due to the short stature
  - Delay in pubertal changes (sexual characteristics and growth spurt) due to delayed bone age
  - Hypoglycemia (in the newborn period)
  - Osteopenia
Differential diagnosis

- Constitutional delay of growth and adolescence
- Familial short stature
- Malnutrition
- Intrauterine growth retardation
- Renal failure
- Inflammatory bowel disease
- Celiac sprue
- Hypo-or achondroplasia
- Turner syndrome
- Russell-Silver syndrome
- Prader-Willi syndrome
- Cystic fibrosis
- Congenital heart disease
- Hypothyroidism
- Hypercortisolism
**Question**: Do girls with short stature who are discovered to have a form of turner syndrome show classic features of turner syndrome?

**Significance**: These girls show more subtle features of turner syndrome such as wide spaced breasts, scoliosis; marked short stature, and commonly delayed puberty. Rarely do such girls show a webbed neck, or lymph edema.
Physical examination

- Measure accurate weight and height with wall stadiometer
- Look for signs of syndromes, chronic disease, or malnutrition
- Evaluate tanner stages of pubertal development
- Check males for micropenis (especially newborns)

Classic GH deficient patient has:

- Protrusion of the frontal bones (frontal bossing)
- Midline facial defects such as poor development of nasal bridge and single central maxillary incisor
- Thin hair
- Poor nail growth
- High pitched voice
- Truncal obesity and relative adiposity
- Cherubic facies
- Dental development delayed
Procedure

- Calculate dental age based on tooth eruption
- Quantify penile and testicular sizes:
  - Small penis in GH deficiency
  - Testicular size (volume using prader beads)
- Palpate for submucosal cleft palate
- Test visual fields
- Calculate growth velocity between growth measurement
Laboratory Aids

- Specific Tests
  - Test: Growth factors
  - Significance: IGF-I and IGFBP-3 (insulin like growth factor binding protein-3) production is regulated directly by GH
  - Test: GH provocative testing
  - Significance: A random GH level is generally of minimal value to diagnose GH deficiency because beyond the neonatal period, GH is only secreted in brief pulses especially during deep sleep (at night)
Nonspecific tests

- Growth factors and the following general tests should be used to screen for common causes of poor growth before embarking on GH provocative testing
- CBC with differential
- Sedimentation rate: Looking for inflammatory processes
- Hepatic and renal function tests
- Chromosomes in females (to exclude turner syndrome)
- Thyroid function tests

Imaging

- Bone age: radiography of left hand and wrist
- If proven GH deficient, head MRI to look for central nervous system tumor
Requirements for Testing

- All blood tests, except GH provocative testing, do not require any form of preparation.
Possible Conflicts

- Usefully not given in cancer patients until 1 year has elapsed without recurrence
Follow-Up of Growth Hormone Therapy

When to Except Improvement

- Immediate effect on hypoglycemia
- Growth velocity improves within 3 to 6 months

Signs to watch for

- Pseudotumor cerebri (headache, vision problems)
- Slipped capital femoral epiphysis (SCFE)
- Theoretically, increased risk of leukemia (though most studies suggest no significant increased risk)
Pitfalls

- Children with constitutional or pubertal delay show poor growth prior to starting puberty mimicking GH deficiency.
- GH provocative testing may yield false-positive or false-negative results. 20% of normal children will fail at least one GH provocative test; obese but otherwise normal children are more likely to fail provocative GH testing.
- Malnutrition can cause low IGF-I.
- Psychosocial deprivation mimics GH deficiency. Such deprived patients may have low growth factors and respond poorly to GH provocative testing.
- rhGH therapy is associated with idiopathic intracranial hypertension (pseudotumor cerebri). This side effect is often transient, is usually reversible when the rhGH dose is decreased, and does not require cessation of therapy in all cases.
- Carefully evaluate any limp and knee or hip pain in patients on rhGH therapy because these symptoms may herald the onset of SCFE. SCFE mandates orthopedic consultation.
- There has been a slightly increased incidence of leukemia in rhGH treated children. It is controversial whether this is due to rhGH or predisposing factors in these children (e.g., selection bias when studying children with growth failure).
<table>
<thead>
<tr>
<th>Finding</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal upper/lower segment ratio</td>
<td>Primary short stature</td>
</tr>
<tr>
<td>Low weight/height ratio</td>
<td>Points toward malnutrition</td>
</tr>
<tr>
<td>Edema</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Frontal bossing, flat nasal bridge, and truncal fat deposition</td>
<td>GH deficiency</td>
</tr>
<tr>
<td>Abdominal distention and gluteal wasting</td>
<td>Malabsorption and celiac disease</td>
</tr>
<tr>
<td>Webbed neck, increased carrying angle, shield chest</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Smooth tongue</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Round face, ear lobe abnormality, and mental retardation</td>
<td>Pseudohypoparathyroidism</td>
</tr>
<tr>
<td>Temporal thinning of the hair, sparse hair, dry hair</td>
<td>Hypothyroidism, GH deficiency hypopituitarism</td>
</tr>
<tr>
<td>Delayed pubertal maturation</td>
<td>Turner syndrome, constitutinal delay, hypopituitarism, hypothyroidism, inflammatory bowel disease, chronic renal disease</td>
</tr>
<tr>
<td>Leg bowing, rachitic rosary widening of wrists</td>
<td>Rickets, malabsorptin</td>
</tr>
</tbody>
</table>
# Average weight

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight in Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>3.25</td>
</tr>
<tr>
<td>6 months</td>
<td>7</td>
</tr>
<tr>
<td>1 year</td>
<td>10</td>
</tr>
<tr>
<td>2 years</td>
<td>12</td>
</tr>
<tr>
<td>3 years</td>
<td>14</td>
</tr>
<tr>
<td>4-10 years</td>
<td>((\text{Age} \times 2) + 8) (e.e. 5 years = 18 kg)</td>
</tr>
</tbody>
</table>
## Average Height [Length]

<table>
<thead>
<tr>
<th>Age</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>50</td>
</tr>
<tr>
<td>6 months</td>
<td>65</td>
</tr>
<tr>
<td>1 year</td>
<td>75</td>
</tr>
<tr>
<td>2 years</td>
<td>85</td>
</tr>
<tr>
<td>3 years</td>
<td>95</td>
</tr>
<tr>
<td>4 years</td>
<td>100</td>
</tr>
<tr>
<td>4-10</td>
<td>100+6 cm per year over 4</td>
</tr>
</tbody>
</table>
Growth Velocity

- It is the rate at which the child grows over a period of time: Beyond the neonatal and infancy period, rather than weight, it is the height that is more useful as an indicator of growth, especially when two measurement are recorded at an interval of about 6 months.
- Growth velocity oscillates around 50th centile.
- Formula for growth velocity (GV):
  \[ GV \text{ (cm)} = \text{initial height (cm)} - \text{height (cm) at next measurement} \div \text{time period between two measurements (years)} \]
Body Ratios

- Upper/lower segments ratio (as measured from the pubis at birth is 1.7:1. With the greater increase in the length of the legs compared to the trunk, by the age of 10 to 12 years the ratio becomes approximately 1:1.

- Stem Stature Index: It refers to the sitting height (Crown-rump length) as a percentage of the total height or recumbent length. It is 70 at birth, 66 at 6 months, 64 at 1 year, 61 at 2 year, 58 at 3 years, 55 at 5 years, 52 at puberty and 53 to 54 at 20 years.

- Arm Span: It is the distance between tips of middle fingers when the arms are outstretched. It is equal to height at 10 years. In earlier years, it is 1 to 2 cm less than the length/height. After 12 years, it is 1-2 cm more than height.
## Head Circumference

<table>
<thead>
<tr>
<th>Age</th>
<th>in cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>35</td>
</tr>
<tr>
<td>6 months</td>
<td>44</td>
</tr>
<tr>
<td>1 year</td>
<td>47</td>
</tr>
<tr>
<td>2 years</td>
<td>49</td>
</tr>
<tr>
<td>3 years</td>
<td>50</td>
</tr>
<tr>
<td>5 years</td>
<td>52</td>
</tr>
<tr>
<td>Adult</td>
<td>56</td>
</tr>
</tbody>
</table>
Problem

- Severe growth failure starting in infancy
- Neonatal or later hypoglycaemia
- Prolonged neonatal jaundice
- Micropenis and/or cryptorchidism
- Collapse in association with hyponatraemia
- Thirst, polyuria and hypernatraemia

Diagnosis

- Congenital hypopituitarism (multiple pituitary hormone deficiency)
Problem

- A girl whose height at age 7 years is inappropriately low for parental stature
- Past history of recurrent otitis media
- Low hair line
- Multiple cutaneous pigmented naevi
- Narrow nail beds

Diagnosis

- Turner syndrome
Problem

- 15 years old boy concerned by lack of pubertal progress
- Associated behavioural problems including aggression
- Normal general health and keen footballer
- Height in 2-9<sup>th</sup> centile channel
- Normal prepubertal sized penis
- Testicular volumes 6-8 ml

**Diagnosis**

- Constitutional delay of growth and puberty (CDGP)
Problem

- A 14 years old girl with breast stage 2 but no additional pubertal features
- Height 156 cm (25th centile), weight 45 kg (10th centile)
- Healthy competitive swimmer
- Pelvic ultrasound showing multicystic changes of ovaries and uterus of length 3.5 cm
- Prepubertal baseline levels of oestradiol, LH, FSH, Prolactin
- Normal thyroxine, TSH levels
- Normal female keryotype

Diagnosis

- Constitutinal or exercise induced delay of puberty