Chapter 8

Endocrinology

Contents :

HYPOTHYROIDISM

Hypothyroidism can be congenital or acquired, and both may be goitrous or non goitrous.

In congenital hypothyroidism "cretinism", the disorder is believed to have been present before birth.

In acquired or juvenile hypothyroidism, a previously normal child develops thyroid deficiency.

CONGENITAL HYPOTHYROIDISM (Cretinism)

Definition:

Congenital deficiency of thyroid hormone (TH) since fetal life.

Background:

Thyroid hormone deficiency can occur because of:

- An anatomic defect in the thyroid gland,
- An inborn error of thyroid metabolism,
- Iodine deficiency.

Epidemiology:

It occurs 1 in 4000 live births worldwide.

Female: male 2:1

Mortality and morbidity:

Profound mental retardation is the most serious effect of untreated congenital hypothyroidism.

Etiology:

I- Primary Hypothyroidism (Diseases in thyroid gland)

1- Non-goitrous cretinism (Thyroid dysgenesis):

- Occurs in about 90% of cases, and is due to thyroid gland dysgenesis (Aplasia, hypoplasia, or an ectopic gland).
- Most cases are sporadic, rarely are familial.
- Female to male ratio is 2:1.
- Hypoplastic thyroid may lie anywhere between the base of the tongue and the normal position of the gland in the neck.

2- Goitrous cretinism:

It occurs in about 10% of cases. It may be either transient or permanent hypothyroidism.

A- Transient hypothyroidism may be due to:

1- Endemic iodide deficiency causing endemic goiter in the mother.

2- Maternal ingestion of antithyroid drugs or iodine containing drugs during pregnancy.

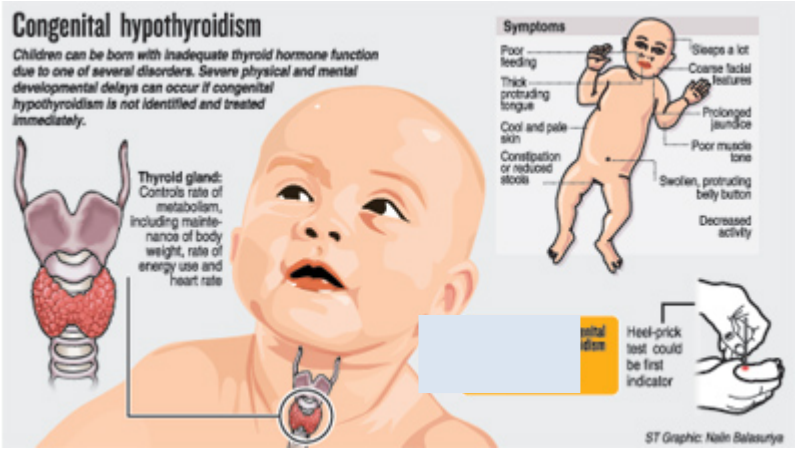
B- Permanent hypothyroidism (Thyroid dyshormonogenesis): It may be caused by deficiency of any enzyme needed to synthesize thyroxine. It is one of inborn error of metabolism which is usually autosomal recessive genetic disease

II-Secondary Hypothyroidism: (Disease in Pituitary gland)

III-Tertiary Hypothyroidism: (Disease in Hypothalamus)

Clinical manifestations:

I- Presentation in neonatal period:



A) Most of the affected infants are asymptomatic at birth and hence the importance of neonatal screening for hypothyroidism. Symptoms develop weeks or months after birth. This is due to partial correction of thyroxine (T_4) deficiency by the transplacental transfer of T_4 from mother to fetus.

B) In severe cases, the early signs of congenital hypothyroidism include:

- Large-sized baby at birth.
- Prolonged physiologic jaundice owing to delayed maturation of glucuronyl transferase enzyme responsible for Bilirubin glucuronosylation.
- The infant sleeps much and cries little.
- Poor appetite and choking spells during nursing.

- Constipation.
- Cold mottled skin especially over the limbs, with or without edema or myxedema.
- Wide anterior fontanel.
- Posterior fontanel is open and large.
- Coarse, and may be ugly facies.
- Goiter may be detected in some cases.

Diagnosis at this period depends on a high degree of suspicion and serum T_4 estimation.

II- Presentation of untreated hypothyroidism during infancy and childhood:

Physical features:

- Facies: The face gradually becomes puffy, ugly, with wrinkled hairy forehead, large protruding tongue, thick lips, and small eyes with narrow palpebral fissures.
- Dry scalp hair, thick short neck with supraclavicular deposits of fat.
- Hoarse cry and voice.
- Hands broad and thick, fingers are short.
- Myxedema in eyelids, dorsum of hand and genitalia.
- Skin is pale, cold, and scaly with little perspiration.
- Short stature, mainly due to short lower limbs.
- Reduced heart rate and low body temperature.
- Delayed dentition and wide anterior fontanel.

Developmental retardation:

- Delayed milestones of development of variable degrees e.g., head support, social smile, sitting, standing, speech …etc.
- Retarded and defective brain development: thyroid hormone is essential for the maturation of brain function during the first two years of life. Congenital hypothyroidism will lead to irreversible brain damage and mental retardation of varying severity if diagnosis and adequate treatment are delayed beyond the first 2-3 months of life.
- Delayed sexual maturation.

Ectopic thyroid hypoplastic tissue:

- This may provide adequate amounts of thyroxine for many months or years.
- Manifestations of inadequate formation are in the form of abnormal physical features mentioned above without affection of intelligence or learning.
- The ectopic thyroid gland may be detected sublingually or as thyroglossal duct cyst or subhyoid median thyroid.

INVESTIGATIONS:

It is important to establish the diagnosis and to start therapy as soon after birth as possible because the risk of brain damage increases when the treatment is delayed.

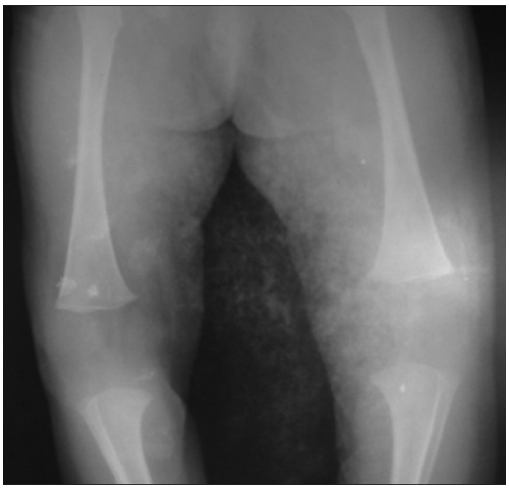
1- Neonatal screening:

- This is a major advance in early diagnosis of neonatal hypothyroidism. A drop of blood obtained by heel prick at 7th day of life is placed on filter paper and sent to a central laboratory. A serum TSH more than 20 micro units / ml (uU / ml) or T_4 less than 6 microgram / dl (ug / dl) is suggestive of hypothyroidism. The diagnosis is confirmed by repeating hormone analysis.
- Neonatal screening may miss 10 % of cases of congenital hypothyroidism, hence the importance of careful observation and critical observation.

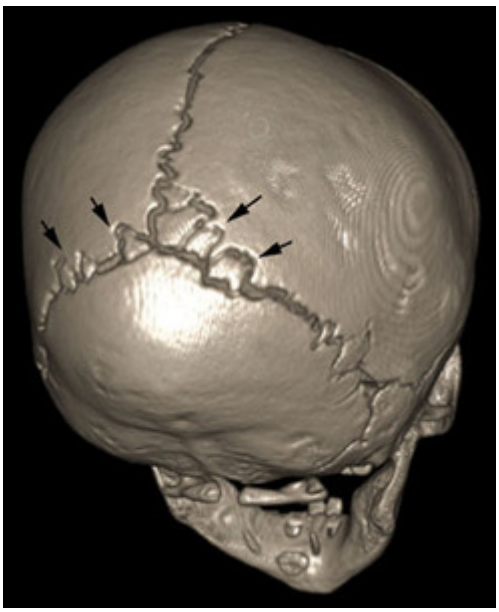
2- Thyroid function will show decreased T_4 (normal 5-15 ug / dl) and increased TSH (normal up to 6 uU / ml).

3- Radiological examination:

- Limbs: delayed bone age and epiphyseal dysgenesis. Absent epiphyses of lower end of femur and upper end of tibia. (epiphyses have multiple foci of ossification)



- Skull: large fontanel and wide sutures, wormian (intra sutural) bones are common.



4- ECG may show low voltage of P, QRS and T waves.

5- Scintigraphic (Isotope) study: using ^{125}**I** or **technetium** ^{99}**Tc** can differentiate between aplasia, ectopic thyroid (abnormal location) and defects in thyroid synthesis.

Differential Diagnosis:

I- During the first 2 months of life:

- Causes of prolonged neonatal jaundice.
- Causes of constipation.
- Causes of edema or sclerema.
- Causes of hypothermia.

II- Later on:

- Causes of developmental retardation e.g., Down syndrome.
- Causes of short stature.

Prognosis:

1- Early diagnosis and adequate treatment from the early weeks of life results in normal physical and mental development.

2- Delay in diagnosis, inadequate treatment or neglect of treatment of cases beyond the first 2-3 months of life result in variable degrees of mental retardation.

3- When onset of hypothyroidism occurs after 2years of age the prognosis is much better. The IQ may be returned to pre-disease level.

Treatment:

Sodium L-thyroxine by (ELtroxin ®)

1. The dose

Age	Dose	Comment
Neonate	10-15µg /kg/day.	The doses are given orally on the morning. Thyroxine tablet should be crushed and fed directly to the infant.
First 2 years	6-8 µg /kg/day	
Older children	4 µg /kg/day	
Adults	2 µg /kg/day	

The above doses should maintain serum T4 level at 12-15 µg / dL, and TSH below 5 uU / ml, and should give normal bone age.

2. Transient hypothyroidism

Infants with endemic iodine deficiency or where their mothers ingested anti-thyroid drugs may have transient hypothyroidism, and in this condition, it is advised that L-thyroxine treatment is discontinued for 3-4 weeks when the child is > 3 years old, If this results in reduction of serum T4 and marked rise of TSH, it confirms the diagnosis of permanent hypothyroidism necessitating lifelong treatment.

3. The response to treatment can be evaluated by:

- Clinical assessment:

√ GIT: constipation or diarrhea,

√ Pulse: Tachycardia or bradycardia

√ Appetite

√ Growth rate

- Investigations:

√ serum T4 level at 12-15 µg / dL,

√ TSH below 5 uU / ml,

√ Should give normal bone age.

4. Follow up of the treatment: is done by:

- Clinical assessment
- Repeated measurement of plasma levels of T_4 and TSH:

1 - At 1 month after initiation of treatment.

2 - Every 2 months during 1st year.

3 - Every 3 months between 1-3 years.

4 - Every 6 months until growth is complete

L-thyroxine overdoses ➔ diarrhea, fever, tachycardia, excessive sweating, irritability and increased appetite

Prognosis:

Early diagnosis and proper treatment prevents MR. Hypothyroidism occurring after 2 yrs. has a good prognosis (brain is sufficiently mature).

Acquired hypothyroidism

Causes:

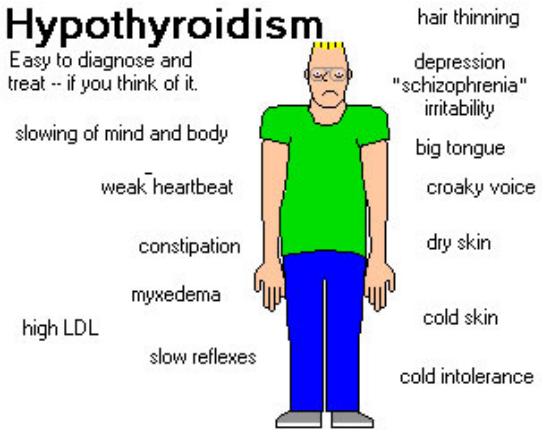
1- Goitrous:

- Hypothalamic-pituitary insufficiency (panhypopituitarism or isolated TSH deficiency).
- Iodine deficiency (endemic goiter).
- Intake of goitrogenic drugs.
- Autoimmune: Hashimoto thyroiditis after an initial stage of hyperthyroidism.

2- Non-goitrous:

- Post-thyroidectomy
- Post-irradiation (e.g. radiotherapy for Hodgkin disease).

Clinical Features:



1. Puffiness of the eyelids
2. Dry, myxedematous skin
3. Low hair line
4. Yellow skin, carotenemia (especially seen in palms of hands and soles of the feet)
5. Anemia refractory to hematinics
6. Decreased activity
7. Decreased school performance
8. Easy fatigability
9. Sense of coldness ,
10. Decreased appetite.
11. Short stature
12. Delayed puberty (the adolescents may not enter the puberty at all).

Investigations:

1. Decreased T_4 (normal 5-15 ug/dl) / increased TSH (normal up to 6 uU / ml).
2. Serum cholesterol and carotene levels are elevated, while serum vitamin A is markedly low.
3. Normocytic normochromic anemia,
4. Bradycardia with low voltage complexes (in all leads)
5. Radiological evidence of delayed bone age and epiphyseal dysgenesis.

The prognosis of the acquired hypothyroidism depends mainly on the underlying cause. Treatment is by L- Thyroxine (See the above table for the doses).

TYPE 1 DIABETES MELLITUS (T1DM)

Definition:

It is a metabolic endocrine disease caused by diminished insulin production and clinically characterized by polyuria, polydipsia, and weight loss, hypovolemia and glycosuria. It is also called insulin dependent diabetes mellitus (IDDM).

Features:

- **Onset is usually < 25 Yrs. old**
- **HLA associated**
- **Autoimmune B cell destruction**
- **Insulin is deficient**

Epidemiology:

Prevalence increases with age: 1/1500 by age of 5 yrs., 1-2 /1000 by school age and 3/1000 by age of 16 years. It occurs in boys and girls equally.

Etiology:

1-Type I diabetes mellitus results from gradual immunologic damage of the β- cells of the pancreatic islets.

2-The immunologic damage requires gene predisposition (HLA) and environmental factors (Viral infections, chemicals, diet, seasonality, and geographic locations).

Clinical Manifestations:

1. Asymptomatic: few cases are detected by routine urine analysis.
2. Mild: presents with enuresis or failure to gain weight.
3. Moderate: presents with polydipsia, polyuria, polyphagia and weight loss.
4. Severe cases may present with ketoacidosis, dehydration increased respiratory effort, acetone breath, mental confusion and coma.

Laboratory Manifestations:

1- Fasting glycosuria with or without ketonuria
2- Fasting plasma glucose over 126 mg/dl.
3- Random plasma glucose (RBS) over 200 mg/dL in the presence of classic symptoms of diabetes.
4- Oral glucose tolerance test (OGTT): plasma glucose after an oral glucose load is > 200 mg/dL.
5- Serum insulin and peptide C levels are reduced
6- Glycosylated hemoglobin (HbA1c) level to estimate degree of glycemic control over the previous 3 month treatment.

Complications:

1. Diabetic ketoacidosis
2. Hypoglycemic coma.
3. Hyperosmolar hyperglycemic state (HHS)
4. Infections may be frequent.
5. Stunting of growth and delayed puberty may occur in poorly controlled diabetic children.
6. Nephropathy, retinopathy and neuropathy due to narrowing of small vessels.
7. Atherosclerosis of large vessels.
8. Other complications due to insulin therapy e.g. hypoglycemia, lipid dystrophy.
9. Psychological and financial problems.

Complications are best avoided by good compliance to insulin therapy, dietetic management and achievement of good glycemic control.

Management:

Mild cases need out patient management and other cases should be hospitalized.

1- **Diet**: balanced and adequate diet for normal growth and development. Consistent timing of 3 main meals and 3 snacks between meals and before bedtime.

2- **Insulin therapy**: in established diabetes the total dose of insulin is usually 0.8-1 Unit/kg/day,

The goal of insulin regimens is to provide more physiologic insulin levels coincide with nutrient absorption and basal levels occur between meals so that there is less between meal insulin action. The basal insulin component provides baseline, between meals, or fasting insulin need. The bolus component provides insulin to cover food requirement and to correct hyperglycemia. The basal component may be provided by either rapid-acting insulin given by the basal rate using an insulin pump, or with once or twice daily injections of NPH (intermediate-acting insulin), determir or glargine (long-acting insulin),.the bolus insulin is provided by rapid –acting insulin which may be given by injections or by the bolus function through an insulin pump

3- **Heavy exercise is avoided, but a moderate exercise is useful.** The child should have a piece of sugar or candy in his pocket and advised to ingest it if he feels hunger, weakness, sweaty or shakiness.

4- **Treatment of complications**.

Type 2 Diabetes Mellitus (T2DM)

It is known as non-insulin dependent diabetes mellitus (NIDDM)

Features:

1. **Onset is usually > 25 Yrs. old.**
2. **Not HLA associated**
3. **No autoimmune B cell destruction**
4. **Insulin is normal or high**
5. **Positive Family history**
6. **Obesity is a risk factor.**

T2 DM is common in African-Americans. Nowadays incidence is increasing due to obesity, and sedentary life. It may present ≈ 10 % of new cases in pediatrics.

Diabetic ketoacidosis (DKA)

Definition:

It is a state of academia induced by excess production of ketoacids (acetoacetic acid and beta butyric acids) due to insulin deficiency.

This condition is characterized by:

1- Blood glucose ≥300 mg/dl + Glycosuria

2- Increased Ketones in blood ± ketonuria

3- Acidosis (ph<7.3), HCO_3^- ≤15 mEq/L

The pathophysiological mechanisms of Ketoacidosis are due to:

1- Insulin deficiency

2- Increase counter regulatory hormones (glucagon, cortisol, catecholamines & growth hormone)

3- Precipitating factors:

- Stress (physical or psychological)
- Infection

Clinical features of ketoacidosis:

1- Polyuria, polydipsia, dehydration + polyphagia

2- Vomiting, abdominal pain (may be severe)

3- Altered consciousness: drowsiness→ coma

4- Air hunger (deep rapid breathing) + acetone odor of breath

5- Evidence of infection may be present.

MANAGEMENT OF DIABETIC KETOACIDOSIS

I. Initial evaluation:

A- Careful history taking and physical examination

B- Laboratory investigations:

1. Complete blood picture
2. Serum electrolytes, ca, P, creatinine, blood urea
3. Glucose (blood & urine) & acetone (urine only)
4. Complete urine analysis
5. Serum bicarbonate, PH, blood gases
6. ECG record (signs of hypokalemia etc.)

II. Supportive measures:

1- Put an IV line and start normal saline infusion immediately

2- Put nasogastric tube and aspirate the stomach

3- Put Foley catheter if the patient is anuric

4- Broad spectrum antibiotics for febrile patients (after obtained cultures)

5- Oxygen for cyanotic or shocked patients and/or with PaO_2 < 80 mmHg

6- Record all patient's data, intakes, outputs and treatments on a flow chart

7- Transfer patient to ICU if bicarbonate is <10, or PH < 7, or if severely ill

III- Fluid therapy:

1- First hour (emergency rehydration)

- Normal saline, 20 ml/kg over the 1st hour
- Repeat if patient has not shown clinical improvement

2- Next 6-12 hours (deficit + maintenance): 5-10 ml/kg/hour

- **Start initially with normal saline**
- Shift to glucose 5% + saline (1:1) when blood glucose drops to < 300 mg/dl
- Potassium is added only when urine flow is satisfactory

3- Oral fluids (carbohydrates & electrolyte mixtures or other liquid diets) can usually be started cautiously within 24 hours and parenteral therapy may be discontinued

IV- Bicarbonate therapy:

1- Bicarbonate therapy is indicated only if blood PH is < 7

2- Dose: 1-2.5 mEq/kg given as IV drip over 2-3 hours, and can be repeated

V- Insulin therapy:

One of the following schedules can be used:

1- Continuous insulin infusion

- Loading dose: regular insulin, 0.1 U/kg IV
- Maintenance : regular insulin, 0.1 U/kg/hour IV

2- Intramuscular:

The intramuscular route should not be used initially in the presence of shock or contraindications such as coagulopathy

- Loading dose: regular insulin, 0.15 U/kg IV or 0.15 U/kg IM.
- Maintenance: regular insulin, 0.1 U/kg/hour IM or SC.

VI- Monitoring schedule:

1- First 6-12 hours:

- Hourly: Blood glucose, urine glucose & ketones, fluid intake and output (urine, etc.)
- Every 2 hours: Serum electrolytes.
- Every 2-4 hours: ECG (for hyperkalemia), creatinine, urea, PH and bicarbonate.

2- Next 12 hours: Laboratory studies as indicated by clinical and biochemical progress

VII- Reassessment of the dose of insulin:

1- Insulin should be given at least every 4-6 hours.

2- Adjust the dose according to rate of fall of blood glucose (no fixed schedule).

3- When patient improves, shift to 6-hourly subcutaneous insulin

(Dose: 0.1-0.5 U/kg according to urine and blood glucose levels)

4- Blood glucose should be kept between 80 and 180 mg/dl.

SHORT STATURE

The child is considered short when his / or her stature (height or length) is below the 5th percentile for age and sex (a height or length less than that of 95 % of children of the same age and sex).

I- Normal variants of short stature:

- These constitute more than 90 % of cases of short stature.
- Two types of "normal variants" are shown in the following table:

		Genetic (familial) Short stature	Constitutional growth delay
Birth length	Birth length	Baby is born small	Baby is born normal in size but grows slowly, so his length is less than 5th percentile over the first 2 years
Maturation	Maturation	Bone age is nearly equal to chronological age Puberty occurs at normal time	Bone age is delayed Delayed puberty and pubertal growth spurt
Family	Family	Short parents	History of delayed puberty.
Final height	Final height	Becomes a short adult	Normal adult height and sexual development

II- Pathological Short stature may be due to:

1- Primary bone disease: skeletal dysplasia: e.g., achondroplasia, Osteogenesis imperfecta and vitamin D resistant rickets.

2- Chromosomal anomalies: e.g., Down syndrome, Turner syndrome, and Laurence-Moon-Biedl syndrome.

3- Intrauterine growth retardation: due to maternal Infections, toxins, Malnutrition and severe illness during pregnancy.

4- Under nutrition: PEM, Vitamin D deficiency rickets, and Mineral deficiencies e.g., zinc, iron

5- Chronic system disease: Gastrointestinal disease, Congenital heart disease, Renal disease, Pulmonary disease, Chronic infections, Collagen disease, Liver disease, Mental retardation, Blood disease

6- Endocrine disease: may be

A- Hyperhormonal:

1- Cortisol excess: Cushing syndrome, and prolonged corticosteroid therapy.

2- Androgen excess: Virilizing adrenal hyperplasia (bone age and height become markedly advanced. Premature closure of epiphysis will result in short adult height in untreated or in inadequately treated patient)

B- Hypohormonal:

1- Hypopituitarism

2- Hypothyroidism (congenital or acquired),

3- Type 1 diabetes mellitus

Evaluation of short stature:

1 - History: Prenatal, neonatal, and during infancy and childhood.

2 - Review of systems: cardiovascular, gastrointestinal, renal, endocrine, CNS….etc.

3 - Measurements: Weight, Length / height, upper / lower segment, span, Head circumference Mid-arm circumference, subcutaneous fat thickness (skin fold thickness)

A- Proportionate short stature:

- Normal variants
- Endocrine causes
- Most causes of growth failure in infancy

B- Disproportionate short stature:

- With short limbs e.g., Skeletal dysplasia (achondroplasia), and Osteogenesis imperfecta
- With short trunk: in Mucopolysaccharidosis, and rickets.

4- Physical examination.

1- Recognition of special features of specific endocrine diseases (e.g., cretinism), or dysmorphic syndromes (e.g., Down syndrome, Turner syndrome, achondroplasia).
2- Measurement of blood pressure (increased in renal disease and congenital adrenal hyperplasia).
3- Neck: webbed neck (Turner syndrome), presence of goiter.
4- Heart: congenital heart disease (e.g., large VSD, Fallot's tetralogy).
5- Chest: bronchiectasis, asthma.
6- Abdomen: hepatomegaly (bilharziasis, chronic hepatitis, glycogen storage diseases).
7- CNS: cerebral palsy, mental retardation.
8- Evaluation of developmental skills.

5- Radiological studies:

- ***Bone age:*** It is delayed in constitutional short stature, Malnutrition, Hypothyroidism, and Hypopituitarism. It is advanced in congenital adrenal hyperplasia.
- ***X ray wrist:*** for diagnosis of infantile rickets.
- ***Skeletal survey***: for skeletal dysplasia.

6 - Echocardiography: for suspected heart disease.

7- Laboratory investigations:

1. Karyotyping: for the possibility of chromosomal disease.
2. Thyroid functions (T3, T4, TSH).
3. Serum Ca, P & alkaline phosphatase: for rickets and hypoparathyroidism.
4. Serum albumin, AST & ALT: to exclude malnutrition and hepatic disease.
5. Serum creatinine and electrolytes to exclude renal disease.
6. ESR: increased in chronic diseases e.g., T.B, chronic inflammatory bowel diseases.
7. Sweat chloride test: to exclude cystic fibrosis.
8. Serum antigliadin antibodies to exclude celiac disease.
9. Investigation of growth hormone secretion:
    - Performed only in short children with slow growth velocity in the absence of systemic disease.

- Physiological test: exercise, sleep.
- Pharmacological test: clonidine, glucagon, L dopa, insulin.

Treatment:

1- Treatment of the underlying disease process if possible.

2- Growth hormone for children with growth hormone deficiency.

3- Replacement of other hormonal deficiencies e.g. thyroid hormone.

Normal puberty

Definition

Puberty is a process leading to physical and sexual maturation that involves the development of secondary sexual characteristics as well as growth, changes in body composition and psychosocial maturation.

Normal puberty begins between 8 and 14 years of age in girls and between 9 and 14 years of age in boys

Normal Development

Two processes contribute to the physical manifestations of puberty: adrenarche and gonadarche.

1] Adrenarche:

It is maturation of adrenal gland which ready to secrete dehydroepiandrosterone (DHEA) and its sulphate. Adrenarche normally occurs between six and eight years of age. It is accompanied by changes in pilosebaceous units, a transient growth spurt and the appearance of axillary and pubic hair in some children, but no sexual development.

2] Gonadarche:

Gonadarche is initiated by the macroneurons of the hypothalamus that secrete Gonadotropin-releasing hormone (GnRH) in a critical pulsatile pattern that regulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary. This pulsatile secretion of Gonadotropin is responsible for enlargement of the gonads and secretion of sex hormones.

Stages of Puberty

1- Girls begin puberty with:

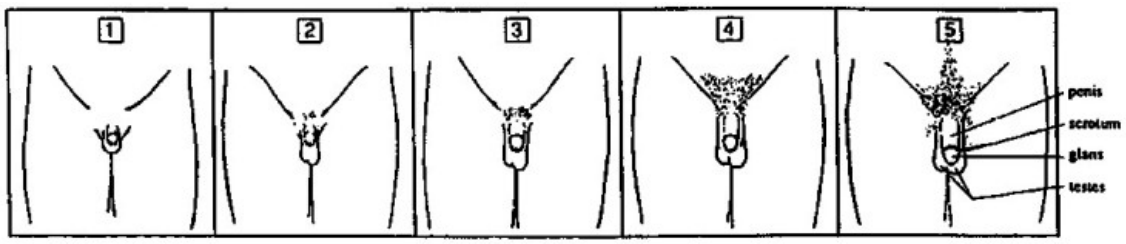
- Appearance of secondary sexual characters:
- Breast buds (10-11yr)
- Skeletal growth (usually the peak height velocity precedes menarche)
- The arrival of pubic hair, then axillary hair
- Appearance of primary sexual character.
- The interval to menarche is usually 2-2.5 years.

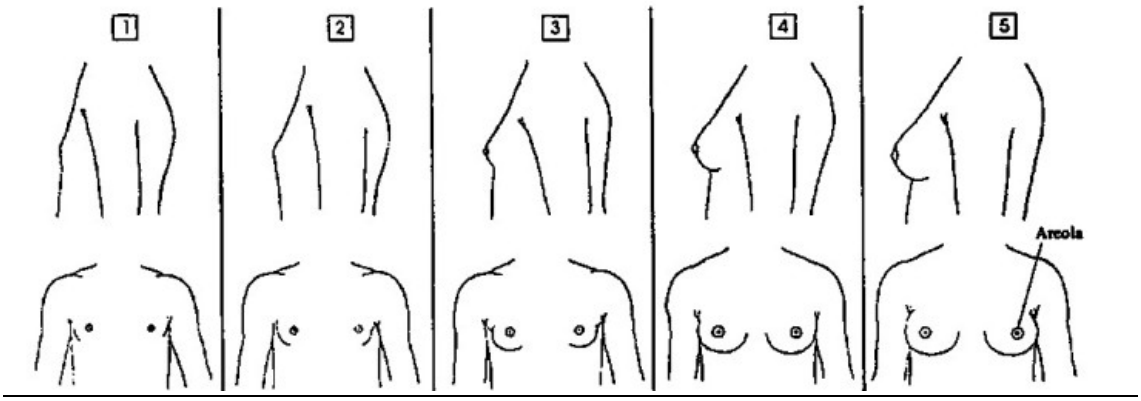
2- In boys puberty begin with

- Appearance of secondary sexual characters:
- Testicular enlargement.
- Thinning and pigmentation of the scrotum.
- The appearance of pubic hair then axillary hair.
- Enlargement of the penis and spermarche (primary sexual character).
- Skeletal and muscle growth are late events in male puberty.

SEX MATURITY STAGES

(TANNER'S STAGES)





A- For Girls:

Tanner stage	Pubic hair	Breast
1	Preadolescent	Preadolescent
2	Sparse, straight, lightly pigmented,	Breast and papilla elevated as small mount
3	Increase in amount, start to curl, darker	Breast and areola enlarged
4	Coarse, curly, abundant but less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

B- For Boys:

Tanner stage	Pubic hair	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Sparse, straight, lightly pigmented	Slight enlargement	Enlarged scrotum, pink
3	Increase in amount, start to curl, darker	Longer	larger
4	Coarse, curly, abundant but less than adult	Larger glans and breadth	Larger, scrotum dark
5	Adult distribution spread to medial surface of thighs	Adult size	Adult size

Factor affecting puberty

1- **Osseous maturation:** the onset of puberty is more closely correlated with osseous maturation than with chronological age.
2- **Race:** black girls have early menarche than white
3- **Environmental factors:** e. g., climate.
4- **Nutrition and general health:** good nutrition and general health leads to early pubertal changes.
5- **Body weight and composition:** obese girls tend to have early menarche. The condition is variable in boys
6- **Genetic factors:** familial

Disorders of Puberty may be either delayed puberty or early puberty (precocious puberty)

Delayed Puberty

Definition:

In girls, delayed puberty is defined as lack of any breast development by 14 years of age or when more than five years pass between initial growth of breast tissue and menarche. In boys, delayed puberty is defined as no testicular enlargement by 14 years of age or the passing of five years between the initial and complete development of the genitalia.

Causes of delayed puberty

1- Constitutional delay (the commonest cause)
2- Gonadotropin deficiency (low plasma levels of LH and FSH)
3- Primary gonadal failure
4- Hypopituitarism due to tumor, infection, idiopathic (panhypopituitarism)
5- Chronic illness, malignancy, chronic infection, chronic debilitating disease.
6- Chromosomal abnormalities: Turner syndrome (45, XO), and Klinefelter syndrome (47, XXY).
7- Miscellaneous condition: anorexia nervosa, extreme athletic persons, idiopathic, malnutrition.