Disorders of theThyroid Gland

The thyroid bilobed shape is recognized by 7 wk of gestation, and characteristic thyroid follicle cell and colloid formation is seen by 10 wk. Thyroglobulin synthesis occurs from 4 wk, iodine trapping occurs by 8-10 wk, and thyroxine (T4) and, to a lesser extent, triiodothyronine (T3) synthesis and secretion occur from 12 wk of gestation.

The main function of the thyroid gland is to synthesize T4 and T3. The only known physiologic role of iodine (or iodide [I−] in its ionized form) is in the synthesis of these hormones; the recommended dietary allowance of iodine is 30 μg/kg/24 hr for infants, 90-120 μg/24 hr for children, and 150 μg/24 hr for adolescents and adults.

The metabolic potency of T3 is 3-4 times that of T4. In adults, the thyroid produces approximately 100 μg of T4 and 20 μg of T3 daily.Only 20% of circulating T3 is secreted by the thyroid; the remainder is produced by deiodination of T4 in the liver, kidney, and other extrathyroidal tissues by type I 5′-deiodinase

The level of T3 in blood is one fiftieth that of T4, but T3 is the physiologically active thyroid hormone.

Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate,lipid, and vitamin metabolism

Approximately 70% of the circulating T4 is firmly bound to T4- binding globulin (TBG). Less-important carriers are T4-binding prealbumin, called *transthyretin*, and albumin. Only 0.03% of T4 in serum is not bound and comprises free T4. Approximately 50% of circulating T3 is bound to TBG, and 50% is bound to albumin; 0.30% of T3 is unbound, or free, T3. Because the concentration of TBG is altered in many clinical circumstances, its status must be considered when interpreting total T4 or T3 levels.

The thyroid is regulated by thyroid stimulating glycoprotein produced by anterior pituitary gland (TSH). TSH synthesis and release are stimulated by thyroid releasing hormone (TRH) which is synthesized in the hypothalamus and pituitary gland, an excess of TRH or of TSH result in hypertrophy and hyperplasia of the thyroid cells, increased traping of iodine and increased synthesis of thyroid hormones, exogenous thyroid hormone or increased thyroid hormone synthesis inhibit TSH production.

Maternal T4 plays a role in fetal development, especially that of the brain, before the synthesis of fetal thyroid hormone begins. The fetus of a hypothyroid mother may be at risk for neurologic injury, and a hypothyroid fetus may be partially protected by maternal T4 until delivery. The amount of T4 that crosses the placenta is not sufficient to interfere with a diagnosis of congenital hypothyroidism in the neonate.

Hypothyroidism

Hypothyroidism results from deficient production of thyroid hormone or a defect in thyroid hormone receptor activity. The disorder may be congenital or acquired.

CONGENITAL HYPOTHYROIDISM

Most cases of congenital hypothyroidism are not hereditary and resultfrom thyroid dysgenesis. Some cases are familial; these are usuallycaused by one of the inborn errors of thyroid hormone synthesis (dyshormonogenesis)and may be associated with a goiter. Most infantswith congenital hypothyroidism are detected by newborn screeningprograms in the 1st few wk after birth, before obvious clinical symptomsand signs develop. In infants born in areas with no screeningprogram, severe cases manifest features in the 1st few wk of life, but incases of milder deficiency, manifestations may be delayed for months.

- Epidemiology

The prevalence of congenital hypothyroidism based on nationwide programs for neonatal screening was initially reported at 1 in 4,000infants worldwide.

- AETIOLOGY

Thyroid dysgenesis. [aplasia, hypoplasia, or an ectopic gland] is the most commoncause of congenital hypothyroidism, accounting for 85% of cases; 10% are caused by aninborn error of thyroxin synthesis, and 5% are the result of transplacental maternalthyrotropin-receptor blocking antibody [TRBAb].

- CLINICAL MANIFESTATIONS

- Most infants with congenital hypothyroidism are asymptomatic at birth, even if there is complete agenesis of thyroid gland due to the transplacental passage of moderate amount of maternal T4, which provides fetal levels that are approximately 33% of normal at birth.
- These low serum levels of T4 and concomitantly elevated levels of TSH make it possible to screen and detect hypothyroid neonates.
- The clinician is dependent on neonatal screening tests for the diagnosis of congenital hypothyroidism. Laboratory errors occur, however, and awareness of early symptoms and signs must be maintained.

- Birth weight and length are normal, but head size may be slightly increased because of myxedema of the brain.
- Prolongation of physiologic jaundice, caused by delayed maturation of glucuronide conjugation, may be the earliest sign.
- Feeding difficulties, especially sluggishness, lack of interest, and choking spells during feeding, are often present during the 1stmo of life.
- Respiratory difficulties, due in part to the large tongue, include apneic episodes, noisy respirations, and nasal obstruction.
- Affected infants cry little, sleep much, have poor appetites, and aregenerally sluggish.
- There may be constipation that does not usually respond to treatment.The abdomen is large, and an umbilical hernia is usually present.
- The temperature is subnormal, often less than 35oc [95oF], and the skin, particularly that of the extremities, may be cold and mottled.
- Edema of the genitals and extremities may be present.
- The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusionare common.
- Macrocytic anemia is often present and is refractory to treatment with hematinics.
- Because symptoms appear gradually, the clinical diagnosis is often delayed.
- Approximately 10% of infants with congenital hypothyroidism had associated congenital anomalies: cardiac anomalies are most common, but anomalies of the nervous system andeye have also been reported.
- If congenital hypothyroidism goes undetected and untreated, these manifestationsprogress, retardation of physical and mental development becomes greater during the following months, and by 3-6 months of age the clinical picture is fully developed.
- The child's growth will be stunted, the extremities are short, and the head size is normal or even increased.
- The anterior and posterior fontanels are open widely; observation of this sign at birth may serve as an initial clue to the early recognition of congenital hypothyroidism
- The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids swollen.
- The mouth is kept open, and the thick, broad tongue protrudes.
- Dentition will be delayed.
- The neck is short and thick, and there may be deposits of fat above the clavicles and between the neck and shoulders [buffalo hump].
- The skin is dry and scaly, and there is little perspiration. Myxedema is manifested, particularly in the skin of the eyelids, the back of the hands, and the external genitals. The skin shows general pallor.
- Carotenemia may cause a yellow discoloration of the skin, but the sclera remain white.

- The hairline reaches far down on the forehead, which usually appears wrinkled, especially when the infant cries.
- Development is usually retarded. Hypothyroid infants appear lethargic and are late in learning to sit and stand.
- The voice is hoarse, and they do not learn to talk.
- The degree of physical and mental retardation increases with age.
- Sexual maturation may be delayed.

❖ LABORATARY FINDINGS

• Most newborn screening programs measure levels of T4, followed by measurement of TSH when T4 is low

• Serum levels of T4 or free T4 are low, serum levels of T3 may be normal and are not helpful in the diagnosis.

• If the defect is primary in the thyroid, levels of TSH are elevated, often to greater than 100 mu/l.

• Serum levels of prolactin are elevated, correlating with those of TSH.

• Retardation of osseous development can be shown radiographically at birth in about 60% of congenitally hypothyroid infants and indicates some deprivation of thyroid hormone during intrauterine life.

• The distal femoral epiphysis, normally present at birth, is often absent.

• In undetected and untreated patients, the discrepancy between chronological age and bone age increases.

• U/S examination of the thyroid is helpful, but studies show it may miss some ectopic glands shown by thyroid scan.

• Thyroid scan can help to pinpoint the underlying cause in infants with congenital hypothyroidism, but treatment should not be delayed for this study.

• 123I-sodium iodide is superior to 99mTc-sodium pertechnetate for this purpose.

• The ECG may show low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion.

• In children older than 2 yr of age, the serum cholesterol level is usually elevated.

❖ TREATMENT

Levothyroxine given orally is the treatment of choice.

In neonates, the initial starting dose is 10-15 μg/kg/day Levels of T4 or free T4 and TSH should be monitored at recommended intervals [approximately monthly in the first 6 mo of life, and then every 2-3 mo between 6mo and 2 yr] and maintained in the normal range for age.

Children with hypothyroidism require about 4μg /kg/24 hr, adults require only 2μg/kg/24hr.

❖ PROGNOSIS

• Early diagnosis and adequate treatment from the first weeks of life result in normal linear growth and intelligence comparable with that of unaffected siblings.

• Approximately 20% of children have a neurosensory hearing deficit.

• Without treatment, affected infants are profoundly mentally deficient and growth retarted.

ACQUIRED HYPOTHYROIDISM

Epidemiology

Studies of school-age children report that hypothyroidism occurs inapproximately 0.3%. Subclinical hypothyroidism (TSH>4.5 mU/L, normal T4 or free T4) is more common, occurring inapproximately 2% of adolescents. Acquired hypothyroidism is mostcommonly a result of chronic lymphocytic thyroiditis; 6% of childrenage 12-19 yr have evidence of autoimmune thyroid disease, whichoccurs with a 2 : 1 female : male preponderance.

Etiology

The most common cause of acquired hypothyroidism ischronic lymphocytic (Hashimoto) thyroiditis . **Autoimmunethyroid disease** may be part of polyglandular syndromes;children with

Down and Turner syndrome, possibly Klinefelter syndrome,and celiac disease or diabetes are at higher risk for associatedautoimmune thyroid disease as are those with**autoimmunepolyglandular syndromes (APSs).**

Other causes: Drug-induced(Excess iodide: amiodarone, nutritional supplements, expectorants Anticonvulsants: phenytoin, phenobarbital, valproate Antithyroid drugs: methimazole, propylthiouracil),Postablative(Irradiation, Radioiodine,Thyroidectomy),Systemic infiltrative disease(Cystinosis,Langerhans cell histiocytosis),Hypothalamic-pituitary disease with multiple pituitary hormone deficiencies(Hypothalamic-pituitary tumors (e.g., craniopharyngioma), Meningoencephalitis, Cranial radiation, Head trauma

Clinical Manifestations

Deceleration of growth is usually the first clinical manifestation, but this sign often goes unrecognized .Goiter associated with Hashimoto thyroiditis, which may be a presenting feature,typically is nontender and firm, with a rubbery consistency and apebbly surface. Weight gain is mostly fluid retention (myxedema), nottrue obesity. Myxedematous changes of the skin, constipation, coldintolerance, decreased energy, and an increased need for sleep developinsidiously. Surprisingly, schoolwork and grades usually do not suffer,even in severely hypothyroid children. Additional features include bradycardia,muscle weakness or cramps, nerve entrapment, and ataxia.Osseous maturation is delayed, often strikingly, which is an indicationof the duration of the hypothyroidism. Adolescents typically havedelayed puberty; older adolescent girls manifest menometrorrhagia.Younger children might present with galactorrhea or pseudoprecocious puberty.

Diagnostic Studies

Children with suspected hypothyroidism should undergo measurementof serum free T4 and TSH. Because the normal range for thyroidtests is slightly higher in children than adults, it is important tocompare results to age-specific reference range

Treatment and Prognosis

l-T4 is the treatment of choice in children with hypothyroidism. The dose on a weight basis gradually decreases with age. For children age1-3 yr, the average l-T4 dosage is 4-6 μg/kg/day; for age 3-10 yr,3-5 μg/kg/day; and for age 10-16 yr, 2-4 μg/kg/day. Treatment should be monitored by measuring serum free T4 and TSH every 4-6 mo as well as 6 wk after any change in dosage.

CONGENITAL HYPERTHYROIDISM

AETIOLOG

It occurs in only ≈ 2% of infants born to mothers with a hx of Graves disease due to transplacental passage of thyrotropin receptor– stimulating antibody (TRSAb), but the clinical onset, severity, and course may be modified by the concurrent presence of thyrotropin receptor–blocking antibody (TRBAb) which may delay symptoms for several weeks after birth; and by the transplacental passage of antithyroid drugs taken by the mother may also delay symptoms by 3-4 days. The disorder usually remits spontaneously within 6-12 wk but can persist longer, depending on the levels of TRSAb.

Clinical Manifestations

Prenatal Dx by fetal US can detect fetal tachycardia and goiter. Many of the infants are premature with IUGR; most have goiters. The infant is extremely restless, irritable, and hyperactive and appears anxious and unusually alert. The eyes are opened widely and appear exophthalmic. There may be extreme tachycardia and tachypnea, and the temperature is elevated.

In severely affected infants, there is weight loss (despite a ravenous appetite), HSM, jaundice, HT, and HF. The infant can die if therapy is not instituted promptly. Persistent hyperthyroidism → advanced bone age, frontal bossing, cranial synostosis, microcephaly, and cognitive impairment when Rx is delayed.

Diagnostic Studies

Serum levels of **T4** or **free T4** and **T3** are markedly elevated, and **TSH** is suppressed.

Treatment and Prognosis

Oral propranolol (1-2 mg/kg/day ÷ 3) and methimazole (0.25-1 mg/kg/day given every 12 hr); saturated solution of potassium iodide (1 drop per day) may be added.

If the thyrotoxic state is severe, IV fluid therapy and corticosteroids may be indicated. If HF occurs, digitalization is indicated.

After a euthyroid state is reached, antithyroid medications should be gradually tapered. Most cases remit by 3-4 mo of age.

Rarely, classic neonatal Graves disease does not remit but persists for several years or longer. These children have impressive family histories of Graves disease. Conversely, sometimes, in utero hyperthyroidism appears to suppress the hypothalamic-pituitary-thyroid feedback mechanism → permanent central hypothyroidism, requiring lifelong thyroid hormone treatment.