Disorder of thyroid gland

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The main function of the thyroid gland is to synthesize thyroxine T3 & T4 , the only known physiologic role of iodine is in the synthesis of these hormones. The estimated requirement is 75-150μg/day.
The metabolic potency of T3 is 3-4 times that of T4, only 20% of circulating T3 is secreted by the thyroid, the remainder is produced by deiodination of T4 in the liver and kidney.
T3 carries out most of the physiologic actions of the thyroid hormones, T4 is more abundant but it binds weakly to nuclear receptor and most of it's physiologic effect occur via conversion to T3 . Reliable method now is measuring the level of T3 directly in the blood , it's concentration is 1/50 that of T4.

The thyroid hormone;

1. increases oxygen consumption.
2. stimulate protein synthesis.
3. influences growth and differentiation.
4. affect carbohydrate, lipid and vitamins metabolism.

- The circulating thyroid hormones T3 &T4 are firmly bound to thyroxine-binding proteins of which major one is thyroxine-binding globulin (TBG) less important thyroxine binding pre-albumin TBPA and albumin.

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.

Hypothyrodism

Hypothrodism is result from deficient production of thyroxine hormone may be manifest very early in life. When symptoms appear after a period of apparently normal thyroid function, it may be either truly acquired or only as result of variety of congenital defects in which manifestation of the deficiency is delayed.

Etiologic classification of hypothyrodism

1. deficiency of TRH.
2. deficiency of TSH.
3. deficiency of thyroid hormones.

Aplasia , hypoplasia or ectopic thyroid, developmental, maternal radioiodine, maternal autoimmune diseases.
Defective synthesis of thyroid hormone (goitrous hypothyrodism), iodine traping defect, iodide organization defect, thymoglobulin synthesis defects , iodine deficiency(endemic cretinism).

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Damage to thyroid gland, autoimmune disease (lymphocytic thyroiditis), cystinosis.
Maternal ingestion of medications, iodide, methimazole (neonatal goiter), propylthiouracil.
Iatrogenic, thyroidectomy, drugs (iodode, cobalt lithium) neck irradiation e.g. Hodgkin disease.
End organ defects
TSH (unresponsiveness) AD and AR

Congenital hypothyrodism

Developmental defects of thyroid gland (dysgenesis) are the most common causes of congenital hypothyrodism (90%) of cases.
The incidence is 1/3800-1/4000 infants world wide .
The disorder is usually sporadic but familial cases have been reported.
Twice as many females as males are affected, neonatal screening test is very important for diagnosis.

Clinical manifestation;

Most infants with congenital hypothyroidism are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This situation is attributed to the transplacental passage of moderate amounts of maternal T_4, which provides fetal levels that are approximately 33% of normal at birth. These low serum levels of T_4 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. Congenital hypothyroidism is twice as common in girls as in boys. Before neonatal screening programs, congenital hypothyroidism was rarely recognized in the newborn because the signs and symptoms are usually not sufficiently developed. It can be suspected and the diagnosis established during the early weeks of life if the initial but less characteristic manifestations are recognized. 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, somnolence, and choking spells during nursing, are often present during the 1st mo of life. Respiratory difficulties, due in part to the large tongue, include apneic episodes, noisy respirations, and nasal obstruction. Typical respiratory distress syndrome may also occur. Affected infants cry little, sleep much, have poor appetites, and are generally 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 35°C (95°F), 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 effusion are 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 have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported.

If congenital hypothyroidism goes undetected and untreated, these manifestations progress. Retardation of physical and mental development becomes greater during the following months, and by 3–6 mo of age the clinical picture is fully developed. When there is only partial deficiency of thyroid hormone, the symptoms may be milder, the syndrome incomplete, and the onset delayed. Although breast milk contains significant amounts of thyroid hormones, particularly T_3, it is inadequate to protect the breast-fed infant with congenital hypothyroidism, and it has no effect on neonatal thyroid screening tests.

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. Only 3% of normal newborn infants have a posterior fontanel larger than 0.5 cm. 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. The hands are broad and the fingers short. 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 with a sallow complexion. Carotenemia may cause a yellow discoloration of the skin, but the scleras remain white. The scalp is thickened, and the hair is coarse, brittle, and scanty. 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 or may not take place at all.

The muscles are usually hypotonic, but in rare instances generalized muscular pseudohypertrophy occurs **(Kocher-Debré-Sémélaigne syndrome).** Affected older children may have an athletic appearance because of pseudohypertrophy, particularly in the calf muscles. Its pathogenesis is unknown; nonspecific histochemical and ultrastructural changes seen on muscle biopsy return to normal with treatment. Boys are more prone to development of the syndrome, which has been observed in siblings born to a consanguineous mating. Affected patients have hypothyroidism of longer duration and severity.

Laboratory data

1. serum level of T3&T4 are low or border line , if the defect is primary in the gland level of TSH in the serum is elevated , while if the level of TSH is low , the hypothyrodism is secondary to pituitary or hypothalamic defect.
2. retardation of osseous development can be seen by X-ray at birth in about 60% of hypothyroid infant. Distal femoral epiphysis normally present at birth is often absent. Chest X-ray; cardiac enlargement or pericardial effusion may be present.
3. ECG of low voltage and P &T-waves with decrease amplitude of QRS complex.
4. EEG is frequently of low voltage.
5. children over 2years of age , serum level of cholesterol is usually elevated.
6. scintigraphy is indicated to determine whether there is any thyroid tissue by radioistop iodine study.

Treatment;

Levothyroxine given orally is the treatment of choice. Because 80% of circulating T_3 is formed by monodeiodination of T_4, serum levels of T_4 and T_3 in treated infants return to normal. This is also true in the brain, where 80% of required T_3 is produced locally from T_4. In neonates, the recommended initial starting dose is 10–15 μg/kg (37.5 to 50 μg/24 hr). Newborns with more severe hypothyroidism, as judged by a serum T4 <3 μg/dL, should be started at the higher end of the dosage range. Thyroxine tablets should not be mixed with soy protein formulas or iron, because these can bind T_4 and inhibit its absorption. Levels of T_4or free T_4 and TSH should be monitored at recommended intervals (approximately monthly in the first 6 mo of life, and then every 2–3 mo between 6 mo and 2 yr) and maintained in the normal range for age. Children with hypothyroidism require about 4 μg/kg/24 hr, and adults require only 2 μg/kg/24 hr.

Later, confirmation of the diagnosis may be necessary for some infants to rule out the possibility of transient hypothyroidism. This is unnecessary in infants with proven thyroid ectopia or in those who manifest elevated levels of TSH after 6–12 mo of therapy because of poor compliance or an inadequate dose of T_4. Discontinuation of therapy at about 3 yr of age for 3–4 wk results in a marked increase in TSH levels in children with permanent hypothyroidism.

The only untoward effects of sodium–L-thyroxine are related to its dose. Overtreatment may risk craniosynostosis and temperament problems. An occasional older child (8–13 yr) with acquired hypothyroidism may experience pseudotumor cerebri within the first 4 mo of treatment. In older children, after catch-up growth is complete, the growth rate provides a good index of the adequacy of therapy. Parents should be forewarned about changes in behavior and activity expected with therapy, and special attention must be given to any developmental or neurologic deficits.

Prognosis;

With the advent of neonatal screening programs for detection of congenital hypothyroidism, the prognosis for affected infants has improved dramatically. Early diagnosis and adequate treatment from the first weeks of life result in normal linear growth and intelligence comparable with that of unaffected siblings. Some screening programs report that the most severely affected infants, as judged by the lowest T_4 levels and retarded skeletal maturation, have reduced (5–10 points) IQs and other neuropsychological sequelae, such as incoordination, hypotonia or hypertonia, short attention span, and speech problems. Approximately 20% of children have a neurosensory hearing deficit.
Without treatment, affected infants are profoundly mentally deficient and growth retarded. Thyroid hormone is critical for normal cerebral development in the early postnatal months; biochemical diagnosis must be made soon after birth, and effective treatment must be initiated promptly to prevent irreversible brain damage. Delay in diagnosis, failure to correct initial hypothyroxinemia rapidly, inadequate treatment, and poor compliance in the first 2–3 yr of life result in variable degrees of brain damage.
When onset of hypothyroidism occurs after 2 yr of age, the outlook for normal development is much better even if diagnosis and treatment have been delayed, indicating how much more important thyroid hormone is to the rapidly growing brain of the infant.

Hyperthyroidism

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Hyperthyroidism results from excessive secretion of thyroid hormone during childhood, with few exceptions, is due to Graves disease. **Graves disease** is an autoimmune disorder; production of thyroid-stimulating immunoglobulin (TSI) results in excessive synthesis, release, and peripheral metabolism of thyroid hormones produce the clinical features.

Clinical manifestations:

Hyperthyroidism **Graves disease**; in children is about five times more common in females than in males, with a peak incidence in adolescence, physical signs are;

1. due to increased catecholamine effects;nervousness, palpitations,tachycardia,atrial arrhythmias,systolic hypertension,tremor, and brisk reflexes.
2. Due to hypermetabolism; increased sweating, shiny, smooth skin, heat intolerance, fatigue, weight loss with appetite, increased bowel movement and hyperkiness.
3. Myopathy; weakness, periodic paralysis,cardiac failure.
4. Other features; proptosis, exophthalmos, lid lag , ophthalmopathy, hair loss and inability to concentrate, personality change, goiter, thyroid bruit, onycholysis.
5. Acute thyroid storm ; hyperpyrexia, tachycardia, coma, high-output heart failure and shock.
6. Personality changes, mood instability, and poor school performance are common.
7. The tremor ,anxiety, inability to concentrate, and weight loss may be insidious and confused with a psychological disorder until thyroid function tests reveal the elevated serum free T4 level, serum T4 may remain near normal while serum T3 is selectively elevated (T3 toxicosis).

Treatment

1- Medical therapy consists of propylthiouracil (PTU) to block thyroid hormone synthesis(5-7 mg/kg/24hr PO in divided doses every 8hrs). Propranolol is started if symptoms are severe (2-3mg/kg/24hr orally) to control cardiac manifestations and is tapered as the PTU or methimazole takes effect. PTU usually is continued for 1-2 years because the remission rate is approximately 25% per year.
2- Surgical treatment consist of partial or complete thyroidectomy.
3- Radioiodine (^{131}I) is slower in exerting therapeutic effects, may require repeated dosing and may cause hypothyrodism.

Congenital hyperthyroidism

This disorder results from transplacental passage of maternal TSIs. Irritability, tachycardia(often with signs of cardiac failure simulating cardiomyopathy), polycythemia, craniosynostosis, bone age advancement, poor feeding, and later failure to thrive.
Treatment for severely affected neonate includes oral propranolol at 2-3mg/kg/24hr in divided doses and propylthiouracil 5mg/kg/24hr orally in three divided doses.
Spontaneous resolution usually occurs by 2-3months of age.

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