Written by Donald Yung
Edited by Dianna Louie

Hypothyroidism

Basic Embryology and Anatomy

The thyroid gland consists of two lobes connected by an isthmus and is located anterior to the trachea at the base of the neck. During embryogenesis, thyroid cells migrate caudally from the pharyngeal floor to the fourth pharyngeal pouch, and develop anterior to the trachea.

Basic Physiology

The thyroid gland is primarily responsible for the production of thyroxin (T4) and triiodothyronin (T3). Thyroid hormone production is regulated by the hypothalamus-pituitary-thyroid axis, in which the hypothalamus secretes thyrotropin releasing hormone (TRH) to stimulate the anterior pituitary to release thyroid stimulating hormone (TSH) into the bloodstream. TSH causes the thyroid to produce and release thyroid hormone. Serum T4 modulates TRH and TSH secretion, thus creating a negative feedback loop.

Synthesis of thyroid hormone occurs in thyroid follicular cells and requires the iodination of tyrosine residues. This is mediated by thyroid peroxidise. T3 and T4 are stored within thyroglobulin in the follicular lumen until it is released. TSH causes the liberation of T3 and T4 from thyroglobulin, as well as the uptake and organification of iodide.

Most of the thyroid hormone produced is T4, which binds to thyroid binding globulins in the blood. Inside peripheral tissues, T4 is absorbed and converted into T3, which is more biologically active than T4. Thyroid hormone acts on the nucleus of the cell and modulates gene transcription.

Thyroid hormone is responsible for increasing the basal metabolism, maintaining skeletal muscle mass, inducing CNS development in the fetus, and promoting growth and development.

Classification and Causes of Hypothyroidism

Hypothyroidism is a very common endocrine disease, and may be congenital or acquired. It can also be defined as primary or secondary hypothyroidism depending on the location of the pathology (thyroid or hypothalamus/ pituitary gland, respectively). In infants, the most common cause of hypothyroidism is thyroid dysgenesis, which may range from aplasia to functional ectopic thyroid tissue. In children and adolescents, the most common cause is chronic autoimmune thyroiditis (Hashimoto thyroiditis).

1.1 Common causes of childhood hypothyroidism

Congenital	**Acquired**
Thyroid dysgenesis	CLT (Hashimoto thyroiditis)
Inborn errors of thyroxin synthesis	Iodine deficiency
Maternal antibody-mediated congenital	Drug-induced thyroiditis

hypothyroidism	
Central (hypothalamic-pituitary) hypothyroidism	Secondary to hypoplastic or ectopic thyroid gland
	Euthryroid sick syndrome
	Irradiation of the thyroid gland
	Surgical excision of thyroid

Clinical Presentation of Hypothyroidism

The clinical presentation of hypothyroidism varies depending on the age of the infant/ child.

Newborn Infants (Cretinism)

Most infants with congenital hypothyroidism remain asymptomatic during the neonatal period, and may only present signs and symptoms after age 6-12 weeks. The earliest signs of hypothyroidism may include:

- Prolonged gestation
- Elevated birth weight and head circumference
- Constipation
- Prolonged indirect jaundice
- Poor feeding
- Hypothermia
- Decreased activity level
- Noisy respiration/ reparatory difficulty
- Cyanosis
- Hoarse cry
- Umbilical hernia
- Marked retardation of bone maturation
- Absence of proximal tibial and distal femoral epiphysis

Children and Adolescents

Signs and symptoms of hypothyroidism in children and adolescents are similar to those in adults, in addition to changes in growth patterns. Some of the signs of hypothyroidism may include:

- Goiter
- Retarded growth
- Short stature (declining growth velocity)
- Precocious puberty
- Declining school performance
- Cold intolerance
- Fatigue and lethargy
- Depression
- Dry skin
- Constipation

- Hoarseness
- Weight gain
- Bradycardia
- Myxedema
- Delayed relaxation phase of reflex

Complications of hypothyroidism
- Growth failure
- Mental retardation
- Slowed metabolism
- Impaired memory

Questions to Ask

History
- Take a complete history with special attention to:
- Patient may present with vague symptoms such as lethargy or fatigue
- Past medical history
    - History of thyroid problems
    - Thyroid surgery
    - Radioactive iodine therapy
    - Past or current radiation therapy
- Family history:
    - Thyroid disorders
    - Endocrine disorders
    - Autoimmune disorders
- Medication
    - Lithium
    - Amiodarone

Differential Diagnosis
- Constipation
- Constitutional Growth Delay
- Growth Hormone Deficiency
- Malabsorption Syndromes
- Malnutrition
- Mood Disorder: Depression
- Short Stature

Laboratory Workup

Serum TSH
- It is the most sensitive screening test for hypothyroidism and for diagnosing primary hypothyroidism.

Serum Free T4

- It is a useful test for diagnosing primary hypothyroidism.

Serum Free T3
- This test is not required for the diagnosis of hypothyroidism. However, serum T3 levels are decreased in euthyroid sick syndrome.

Serum antithyroid antibody
- This test is only used to confirm the diagnosis of CLT (Hashitmoto's thyroiditis)

Radioisotope thyroid imaging
- This test is useful for measuring iodine uptake or to screen for ectopic thyroid tissue.

Newborn Screening in BC

In British Columbia, all newborns are screened for congenital hypothyroidism, in addition to 21 other congenital disorders. The parent(s)/ guardian(s) may choose to decline the newborn screening test. If this occurs, the physician should be present to answer any questions and recommend newborn screening a second time.

Blood is taken from a heel prick and is collected on a blood spot card for analysis. The sample should be allowed to dry in room temperature for at least three hours. It is recommended the test to be performed between 24 and 48 hours after birth or before the infant is discharged, with a repeat sample by two weeks of age. All samples are sent to the Newborn Screening Laboratory at BC Children's Hospital for analysis.

Treatment and Follow Up

Hypothyroidism is treated by thyroid replacement therapy. Levothyroixine, a synthetic thyroid hormone, is the primary drug of choice.

In newborns, treatment should be started immediately after diagnosis to prevent developmental complications. Newborns not treated within 6 weeks of life are at a significantly higher risk of developmental retardation. TSH and T4 levels should be tested monthly until normalized. Afterwards, TSH is measured once every 3 months until the patient is 3 years of age, and every 6 months thereafter.

About 20% of children with chronic autoimmune thyroiditis may become euthyroid later in life. After the completion of puberty, patient can undergo a six month trial off thyroid replacement medication to see if they can remain euthyroid without treatment. If hypothyroidism occurs, the patient should resume and continue therapy for life

Rarely, surgery may be required to treat extremely large goitres. However, the primary treatment for resolving the goitre is T4 replacement therapy.

Conclusion

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Hypothyroidism is a common endocrinological disorder with many different etiologies. In infants, it is primarily due to congenital thyroid dysgenesis, while in children, it is primarily due to chronic autoimmune thyroiditis. Hypothyroidism may present with abnormalities in metabolism and development. If left untreated the patient may have developmental delays. Diagnosis relies on a detailed history and physical exam to illicit potential causes of hypothyroidism. Key laboratory tests are serum TSH and free T4 levels. Treatment is through thyroid replacement therapy and should begin immediately to prevent development complications, with TSH and T4 levels being monitored regularly. Therapy is continued throughout life, although in some cases the patient may become euthymic after puberty.

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