Hypothyroidism

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Objectives   After completing this article, readers should be able to:

1. Describe the classification and causes of congenital and acquired hypothyroidism during infancy, childhood, and adolescence.
2. Compare the presenting clinical symptoms and signs of hypothyroidism based on patient age, duration of disease, and cause of hypothyroidism.
3. Delineate the laboratory tests used in the diagnosis and management of hypothyroidism, and select those tests required for diagnosis and management in children.
4. Understand the interpretation of laboratory test results related to the thyroid gland and its diseases and the pitfalls that arise from laboratory test results that seem incompatible with specific thyroid diseases.
5. Characterize the value of one or two tests, the serum thyroid-stimulating hormone (TSH) and free thyroxine (T4), in the diagnosis and management of primary and central hypothyroidism.
6. Describe the limitations of the analog free T4 test compared with the "gold-standard" direct dialyzable free T4 (DDFT4) test and the importance of using the DDFT4 test to diagnose central hypothyroidism and hypothyroidism for patients who are prescribed specific drugs and diseases that may interfere with thyroid tests.
7. Delineate the prognosis for patients who have primary and central hypothyroidism and the variable influences that age at diagnosis and duration of disease prior to diagnosis have on outcome.

Definitions

Hypothyroidism is a deficiency in thyroid hormone secretion by the thyroid gland and a reduction of thyroid hormone action at the cellular level. The two major forms in children are: 1) congenital hypothyroidism (CH), a group of diseases that develops at conception or during gestation and is present at birth; and 2) acquired hypothyroidism (AH), diseases that have an onset usually after 6 months of age (Table 1). Two major subcategories are: 1) primary hypothyroidism, a decrease in thyroid hormone secretion caused by a damaged, defective, or absent thyroid gland; and 2) hypothalamic and pituitary hypothyroidism, or central hypothyroidism, a failure of the mechanisms that stimulate thyroid-stimulating hormone (TSH) synthesis, secretion, and biologic action. TSH stimulates iodine uptake and synthesis of the thyroid hormones thyroxine (T4) and triiodothyronine (T3).

Epidemiology

Most cases of CH are sporadic. Only about 10% to 15% are caused by inherited defects in thyroid gland stimulation, thyroid hormone synthesis (hormonogenesis), or peripheral action. CH occurs worldwide in 1 in 3,500 to 4,000 newborns when there is normal iodine nutrition in the population and more often when iodine deficiency exists. Girls are affected in sporadic forms twice as often as boys, and the disease is more common among Hispanic infants. In familial forms, an equal number of males and females are affected because the

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Table 1. Causes of Hypothyroidism

Congenital Hypothyroidism

- Permanent Sporadic Hypothyroidism
  - Thyroid dysgenesis
    - Athyreosis (agenesis)
    - Ectopia
    - Hypoplasia
  - Iatrogenic
    - Maternal exposure to ^{131}I-iodine
  - Congenital toxoplasmosis
  - Genetic defects in embryogenesis
    - PAX8, TTF1, TTF2
  - Congenital nephrosis
  - Idiopathic hyperthyrotropinemia
    - (Subclinical hypothyroidism of infancy)
      - Isolated
      - Down syndrome
  - Idiopathic primary hypothyroidism
- Permanent Familial Hypothyroidism
  - Dyshormonogenesis
    - Beta thyroid-stimulating hormone (TSH) loss-of-function mutations
    - TSH receptor loss-of-function mutations, known as TSH
    - Unresponsiveness with mild-to-severe hypothyroidism
    - Iodide trapping defect (sodium iodide symporter mutations)
    - Iodide oxidation defects
      - Pendred syndrome (Pendrin mutations)
      - Thyroperoxidase mutations
    - Thyroglobulin synthetic defects
    - Iodotyrosine deiodinase defect
- Permanent Hypothalamic–Pituitary Hypothyroidism
  - Multiple hypothalamic hormone deficiencies
    - Idiopathic
    - Familial
    - Associated with midline central nervous system anatomic defects
  - Isolated thyrotropin-releasing hormone (TSH) deficiency
  - Isolated TSH deficiency
- Transient Hypothyroidism
  - Iodine deficiency
    - Nutritional
    - Congenital nephrosis
  - Iatrognic
    - Maternal or neonatal exposure to iodine
    - Maternal antithyroid drug therapy
  - Maternal TSH receptor-blocking antibodies
    - Maternal chronic autoimmune thyroiditis
  - Transient dyshormonogenesis
    - Oxidation defect
  - Accelerated degradation
    - Large hemangiomas with type 3 deiodinase activity
    - Medications

Acquired Hypothyroidism

- Late-onset, mild congenital hypothyroidism
  - Ectopic thyroid dysgenesis
  - Familial thyroid dyshormonogenesis
  - Peripheral resistance to thyroid hormone action
- Acquired primary hypothyroidism
  - Chronic autoimmune thyroiditis
    - Lymphocytic thyroiditis of childhood and adolescence with thyromegaly
    - Hashimoto thyroiditis with thyromegaly (struma lymphomatosa)
    - Chronic fibrous variant
    - Acquired autoimmune-mediated infantile hypothyroidism
  - Drug-induced hypothyroidism
    - Antithyroid drugs (propylthiouracil, methimazole, carbimazole)
    - Lithium (therapeutic doses to treat bipolar diseases)
  - Endemic goiter
    - Iodine deficiency with or without selenium deficiency
    - Environmental goitrogens
  - Irradiation of the thyroid
    - Therapeutic radioiodine
    - External irradiation of nonthyroid tumors
  - Surgical excision
  - Subacute thyroiditis: transient phase

mode of inheritance is autosomal recessive. When the mother is either iodine-deficient or exposed to excessive amounts of iodine, the infant often has a goiter with or without hypothyroidism that persists until exposure to deficient or excessive iodine is corrected.

Most cases of AH occur in females who have autoimmune diseases. The incidence of thyroiditis during adolescence approximates 1% to 2%. AH may occur: 1) as autoimmune thyroid disease only; 2) in association with other autoimmune diseases, such as type 1 (insulin-dependent) diabetes mellitus, alopecia, vitiligo, Addison disease, rheumatoid arthritis, and lupus erythematous in the child or family members; and 3) in association with other diseases, such as Down syndrome and Turner syndrome. AH may develop as early as age 6 months; affected infants present with symptoms and signs very similar to those seen in infants who have untreated CH.

Etiology and Pathogenesis

With rare exceptions, the causes of sporadic CH, or thyroid dysgenesis, are not known. Thyroid dysgenesis is classified by the anatomic presentation as athyreosis, ectopia (ectopic thyroid dysgenesis), and hypoplasia. Inherited CH is caused by mutations in the genes that code for specific enzymes and cofactors that are required for thyroid hormonogenesis. These diseases are known as familial thyroid dyshormonogenesis.

Maternal diseases or medications may interfere with thyroid function of the unborn child. A mother who has autoimmune thyroiditis and AH may produce TSH receptor-blocking antibodies that cross the placenta and cause transient fetal hypothyroidism and CH.

Dietary lack of iodine causes endemic goiter and hypothyroidism, both CH (cretinism) and AH. In some areas, iodine, selenium, and iron deficiencies occur alone or coexist. Normal maternal concentrations of T4 (in contrast to T3) are required for normal central nervous system development of the fetus before 11 to 12 weeks of gestation when fetal thyroid hormonogenesis matures. Maternal hypothyroidism during early pregnancy, whether caused by iodine deficiency, autoimmune thyroiditis, inadequate thyroxine therapy after thyroidectomy, or other causes, is associated with decreased intellectual performance among affected progeny.

AH most often is caused by autoimmune thyroiditis, the consequence of abnormalities of the humoral and cellular immune systems that inhibit thyroid hormone secretion and destroy the thyroid parenchyma. The genetically programmed, immune-mediated mechanisms that cause AH are poorly understood, but generate an immune response against the normal thyroid cells that causes inflammation, destruction, and death of thyroid follicular cells, often of sufficient severity to destroy more than 75% of thyroid tissue and cause AH. Other causes of primary AH are uncommon and generally are evident on history (Table 1).

Screening tests are recommended for patients who have a high risk of developing hypothyroidism during childhood and adolescence (Table 1): 1) an elevated serum TSH in primary hypothyroidism, 2) thyroid antibodies to detect thyroiditis before AH develops, and 3) low levels of free thyroxine (FT4) to detect central hypothyroidism. The same methods used to screen every newborn for CH are very cost effective to screen selected high-risk populations at any age.

Clinical Aspects

The common symptoms and signs of hypothyroidism are summarized in Table 2. The appearance of a specific symptom and sign depends on the age when hypothyroidism develops, the duration of the disease, and severity of hypothyroidism. Often, the findings may not be obvious to the parents or the physician until the child's growth velocity declines or hypothyroidism has progressed to a moderate or severe stage.

Infants who have CH are detected by newborn screening programs, where available. Rarely, cases are missed, so clinicians must be aware of the early symptoms and signs of hypothyroidism. An improperly collected and labeled specimen, the absence of a specimen, laboratory error, and various physiologic and pathophysiologic conditions are responsible for missed cases.

On examination of the anterior neck, a symmetric or asymmetric enlargement of the thyroid (goiter) often is detected in AH and may be palpated in some forms of familial dyshormonogenesis during early infancy. A firm or hard consistency of the gland often is present among children who have thyroiditis, and the surface of the gland may be irregular, having a lumpy or nodular consistency. This presentation may raise the concern about thyroid neoplasia (benign adenoma or malignant thyroid carcinoma). However, hypothyroidism is rare among children who have thyroid carcinoma.

Laboratory Tests

Of the many thyroid tests available to clinicians, only a very few are needed to diagnose and manage infants and children who have hypothyroidism. The diagnosis is established by the measurement of serum TSH and free T4 (FT4). A low FT4 value for age is diagnostic of hypothyroidism. An elevated TSH for age is diagnostic of primary hypothyroidism. When serum TSH is normal or

Table 2. Common Symptoms and Signs of Hypothyroidism

Congenital Hypothyroidism

Findings During the First 2 Postnatal Weeks
- Prolonged neonatal jaundice
- Edema of the eyelids, hands, and feet
- Gestation >42 wk
- Birthweight >4 kg
- Poor feeding
- Hypothermia
- Protuberant abdomen
- Large anterior and posterior fontanelles

Findings Beyond Age 1 Month
- Darkened and mottled skin
- Stressful, frequent, and labored breathing
- Failure to gain weight; poor sucking ability
- Decreased stool frequency
- Decreased activity and lethargy

Findings After Age 3 Months
- Umbilical hernia
- Infrequent and hard stools
- Dry skin with carotenemia
- Macroglossia
- Generalized swelling or myxedema
- Hoarse cry

Acquired Hypothyroidism

Findings Between 6 Months and 3 Years of Age
- Deceleration of linear growth
- Coarse facial features
- Dry skin with carotenemia
- Hoarse cry and large tongue
- Umbilical hernia
- Muscular pseudohypertrophy (enlargement of the arm and leg muscles)

Findings During Childhood
- Deceleration of linear growth with or without short stature
- Delay in eruption of teeth and in shedding of primary teeth
- Muscle weakness and pseudohypertrophy (enlargement of the arm and leg muscles)
- Infrequent and hard stools
- Dry skin with carotenemia
- Generalized swelling or myxedema
- Precocious sexual development: breast development without sexual hair in girls; enlarged testes without sexual hair in boys

Findings During Adolescence
- Delayed onset of puberty
- Deceleration of linear growth with or without short stature
- Delay in eruption of teeth and in shedding of primary teeth
- Infrequent and hard stools
- Dry skin with carotenemia
- Galactorrhea (girls)
- Generalized swelling or myxedema

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low in the presence of a low FT4, the diagnosis most likely is hypothalamic or pituitary (central) hypothyroidism. Occasionally, children who have a mildly elevated serum TSH level (<20 mU/L) by immunoassay may have hypothalamic hypothyroidism. In this situation, the TSH molecule is glycosylated incompletely because of a deficiency in thyrotropin-releasing hormone secretion and has reduced biologic activity. Because the immunoassay measures the alpha and beta chains of the peptide instead of biologic activity, the TSH value may be elevated despite reduced biologic activity.

Through the use of newborn screening, the diagnosis of CH is suspected in most infants within 1 week after birth. When the screening TSH value is elevated, confirmatory serum tests are required, but treatment should be initiated before the results of the serum tests are available. Other important diagnostic tests include a serum FT4 level; serum thyroglobulin concentration if the thyroid gland is nonpalpable; and, where available, thyroid ultrasonography as the least invasive test or a technetium pertechnetate or iodine-123 scan, which can be per-

formed 2 hours after administration of the isotope. Iodine-131 should not be used in newborns. Thyroxine therapy can be initiated as soon as the serum tests are collected; it does not need to be withheld while awaiting thyroid imaging.

The most common cause of primary AH is autoimmune thyroiditis, and the diagnostic test is the measurement of thyroid antibodies. Elevated titers of either or both thyroid antibodies—thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb)—are diagnostic of thyroiditis. Without clinical evidence of radiation-induced, traumatic, or subacute thyroiditis, where low titers of TPOAb or TGAb may be seen, positive thyroid antibodies establish the diagnosis of autoimmune thyroiditis, especially in the presence of a palpable thyroid gland and physical characteristics of Hashimoto disease.

Certain laboratories continue to offer total T4 and T3 resin uptake (T3RU) tests to determine the estimated or calculated FT4. The measurement of T4 alone often provides misleading results. T4 is bound primarily to

thyroxine-binding globulin (TBG), but it also binds with less affinity to other thyroxine-binding proteins. However, the unbound or free hormone is the biologically active fraction that enters the cell and is converted to the biologic active hormone, T3. Many clinical conditions, drugs, and inherited diseases can interfere with the bound T4 fraction. For example, inherited TBG deficiency or excess or abnormal binding proteins cause low and high total T4 values when the FT4 measurement is normal. Pregnancy or estrogen therapy increases TBG and total T4 values, yet the FT4 level remains normal. Many drugs, especially certain anticonvulsant medications, bind to TBG and compete with T4 for binding sites, causing a low total T4 concentration. Even the combined use of the T4 and T3RU tests may not provide correct results in many of these situations. The FT4 determination by direct dialysis is the most accurate method and the least likely to give false-positive or -negative results from interfering drugs or other substances in serum. The test is available in national reference laboratories and is a very important method for diagnosing central hypothyroidism at any age. Because the test usually is more costly than the so-called analog FT4 tests, most laboratories offer the analog FT4 initially. Certain clinical conditions, such as the nonthyroidal illness syndrome and specific drugs, interfere with the analog FT4 determination. If the laboratory results do not agree with the clinical presentation, measurement of serum TSH and FT4 by direct dialysis should provide definitive results on which the decision to treat may be based.

Diagnosis

There are routine, mandated newborn screening programs for CH in most areas of the Western world. An elevated TSH value on the newborn screening test requires the performance of a confirmatory serum TSH test. Other tests previously described define the cause (inherited or sporadic) and the severity of hypothyroidism. In older infants and children, hypothyroidism is suspected by: 1) the presence of an enlarged thyroid gland (goiter) on examination of the neck, 2) failure to maintain a normal rate of linear growth, 3) the symptoms and the signs of hypothyroidism (Table 2), or 4) family members having thyroid diseases. Routine TSH screening for children at increased risk for hypothyroidism may be the first indication of hypothyroidism in children.

An elevated TSH concentration is the most sensitive confirmation of the diagnosis of thyroid gland failure. A low FT4 level is diagnostic for hypothalamic/pituitary (central) hypothyroidism. Usually, the FT4 level also is low in primary hypothyroidism, except in mild cases. The usual cause of thyroid gland failure is autoimmune thyroiditis; the diagnosis is confirmed by finding thyroid antibodies in the serum. When the TSH value is increased and serum thyroid antibodies are positive, treatment with thyroxine is indicated.

Among patients who have hypothalamic/pituitary hypothyroidism, other pituitary hormone deficiencies are present, such as insufficient growth hormone secretion, low gonadotropins with lack of pubertal development, and less often, low hydrocortisone secretion or high serum prolactin values.

Management

Treatment for hypothyroidism is easy and inexpensive. Levothyroxine (L-thyroxine) is the treatment of choice during infancy and childhood. Although the total daily dose increases about three- to fivefold from infancy to adult life, the daily dose per body weight steadily decreases to an adult dose in adolescence. Treatment must be individualized because thyroxine absorption and metabolism differ among individuals. For this reason, careful initial monitoring of serum TSH and FT4 is very important until the values are normal. After age 3 years, annual measurements of serum TSH for patients who have primary hypothyroidism and FT4 for those who have central hypothyroidism should be an adequate assessment of thyroxine replacement therapy in compliant patients.

L-thyroxine treatment has no complications when the proper dose is prescribed and ingested and TSH and FT4 values are monitored to maintain euthyroid function. There are complications, however, associated with unrecognized or inadequately treated hypothyroidism; the worst outcome occurs if treatment is delayed in early infancy. Severe hypothyroidism before birth and a delay in treatment after birth are associated with an impaired intellect (as determined by intelligence quotient tests) and other neuropsychological abnormalities. After 3 years of age, adverse effects of untreated hypothyroidism occur, but in most cases, they are reversible with adequate treatment. If hypothyroidism is not recognized or is treated inadequately for 6 to 12 months after its onset, a decrease in the linear growth rate and, in many instances, short stature occur. If diagnosis is delayed or treatment is inadequate for years during late childhood and into adolescence, the final adult height will be less than expected despite appropriate treatment. Prolonged hypothyroidism also is associated with high levels of cholesterol, slowing of mental function and school performance, episodic hip or knee pain caused by unilateral

or bilateral slipped capital femoral epiphysis that often requires surgical intervention, and chronic constipation. Except for an attenuation in the expected adult height, these abnormalities should disappear with appropriate treatment.

Thyroxine absorption is impaired by certain drugs, such as iron and calcium medications, as well as by high dietary fiber in food and certain soy-containing infant formulas; in these situations, the dose of exogenous thyroxine must be increased. Similarly, diseases of the intestine that cause malabsorption, such as celiac disease and inflammatory bowel disease, require an increase in the thyroxine dose to maintain euthyroidism. Women during pregnancy and those receiving estrogen therapy for contraception may require higher doses of thyroxine because of the stimulatory effects of estrogen on thyroxine-binding proteins.

Prognosis

The prognosis for normal intellectual and neurologic function and linear growth is excellent for infants who have CH and are treated adequately beginning in the first few postnatal weeks. A delay in the diagnosis and in the institution of adequate thyroxine therapy beyond 3 months of age usually is associated with an increased risk for impaired intellectual function and neuropsychological development.

Children who develop hypothyroidism after 2 or 3 years of age appear to have no permanent intellectual impairment or neurologic deficits. Chronic hypothyroidism and severe growth retardation in older children and adolescents often result in a failure to achieve expected growth potential. The linear growth response to thyroxine therapy in such children frequently is attenuated and may not be accelerated as expected before or during puberty. The magnitude and duration of the attenuation in the linear growth spurt during puberty adversely influence the height percentile achieved as an adult because it is lower than that predicted by growth before the

development of hypothyroidism. This effect can be prevented by early diagnosis of AH through accurate annual measurements of height and calculation of growth velocity, which normally should be at least 5 cm/y (2 in/y) from age 4 years to the onset of puberty. Children at high risk for hypothyroidism, such as children who have Down syndrome and those whose family members have autoimmune thyroid diseases, should receive serum TSH and thyroid antibody tests at the time of their annual physical examinations of the thyroid and height. Maintenance of TSH and FT4 within normal ranges for age assures compliance and adequacy of therapy. These tests may need to be performed more often when previous TSH or FT4 results are abnormal, when compliance is questioned, or if the child is found to have an unexplained deceleration in linear growth.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

11. On a routine annual evaluation, a 13-year-old girl from the Midwest is found to have a diffusely enlarged thyroid gland that is approximately three times the normal size according to World Health Organization criteria. She is active, healthy, clinically euthyroid, and has no other abnormalities on physical examination. The family history discloses that two maternal aunts and two cousins each were told that they had a "goiter." Among the following, the *most* likely cause of this patient's thyroid enlargement is:

    A. Adolescent goiter.
    B. Autoimmune thyroiditis.
    C. Familial thyroid dyshormonogenesis.
    D. Nutritional deficiency goiter.
    E. Thyroid neoplasia.

12. Among the following, the *most* sensitive laboratory test to diagnose primary hypothyroidism is measurement of serum:

    A. Free T4.
    B. Thyroglobulin.
    C. Thyroid antibodies.
    D. Total T3.
    E. TSH.

13. An 8-year-old girl has had a 2-year decline in growth velocity, as determined by plotting her height on a standard growth curve. At age 6 years, her height was at the 60th percentile; at age 7 years, it was at the 40th percentile; and at age 8 years, it was at the 10th percentile. Her parents are of average height. Her history is otherwise unremarkable, and physical examination reveals no abnormalities, although the thyroid gland cannot be palpated. The pair of laboratory tests that would *best* help explain the cause of this patient's recent growth retardation is:

    A. Free T4 and T3.
    B. Growth hormone and blood urea nitrogen.
    C. Thyroid ultrasonography and technetium pertechnetate scan.
    D. T4 and free T3.
    E. TSH and free T4.

14. You receive notification that a male infant in your practice had an elevated TSH level on newborn screening. The *most* important laboratory test to obtain immediately is a measure of:

    A. Free T4.
    B. Thyroglobulin.
    C. Thyroid antibody.
    D. Total T3.
    E. Thyroid-stimulating hormone.

15. Although the prognosis for normal intellectual and neurologic function and linear growth can be excellent for children who have congenital hypothyroidism, delaying treatment beyond which of the following ages is likely to be associated with impairments?

    A. 24 hours.
    B. 2 weeks.
    C. 3 months.
    D. 6 months.
    E. 1 year.