Hypothyroidism

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Educational Gap

Congenital hypothyroidism is one the most common causes of preventable intellectual disability. Awareness that not all cases are detected by the newborn screening is important, particularly because early diagnosis and treatment are essential in preserving cognitive abilities.

Objectives

After completing this article, readers should be able to:

1. Identify the causes of congenital and acquired hypothyroidism in infants and children.
2. Interpret an abnormal newborn screening result and understand indications for further evaluation and treatment.
3. Recognize clinical signs and symptoms of hypothyroidism.
4. Understand the importance of early diagnosis and treatment of congenital hypothyroidism.
5. Understand the presentation, diagnostic process, treatment, and prognosis of Hashimoto thyroiditis.
6. Differentiate thyroid-binding globulin deficiency from central hypothyroidism.
7. Identify sick euthyroid syndrome and other causes of abnormal thyroid function test results.

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ABBREVIATIONS

CH	congenital hypothyroidism
FT_3	free triiodothyronine
FT_4	free thyroxine
HT	Hashimoto thyroiditis
LT_4	levothyroxine
rT_3	reverse triiodothyronine
T1DM	type 1 diabetes mellitus
T_3	total triiodothyronine
T_4	total thyroxine
TBG	thyroid-binding globulin
TBII	thyrotropin-binding inhibitory immunoglobulin

BACKGROUND

The thyroid gland produces hormones that have important functions related to energy metabolism, control of body temperature, growth, bone development, and maturation of the central nervous system, among other metabolic processes throughout the body. The thyroid gland develops from the endodermal pharynx. The gland becomes visible at the beginning of the third week of gestation and starts trapping iodine and secreting thyroid hormones after the tenth week of gestation. Before this, transplacental passage of maternal thyroid hormones is vital for fetal development. Transplacental passage of total thyroxine (T_4) is also evident at the end of the

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gestation, when approximately one-third of maternal T_4 passes to the fetus. Because of the 3.7-day half-life of T4 in the newborn, maternal sources of T4 take between 2 and 3 weeks to be metabolized and excreted. At delivery, exposure to a cold environment causes a surge of thyrotropin within 30 minutes, as high as 160 mIU/L, with a subsequent increase in T_4 and total triiodothyronine (T_3). Thyrotropin decreases significantly by 48 hours after birth, reaching infant levels of less than 10 mIU/L by the fifth day after birth.

DEFINITION

Hypothyroidism is a deficiency in thyroid hormone production by the thyroid gland, with ensuing metabolic and neurologic effects at the cellular level. The most common causes of hypothyroidism in iodine-replete regions of the world are congenital hypothyroidism (CH) and Hashimoto thyroiditis (HT). Hypothyroidism has a wide spectrum of clinical presentations, from transient and subclinical forms to severe cases, the latter with catastrophic neurologic consequences when present in the neonatal period without early diagnosis. Subclinical hypothyroidism is defined as an elevated thyrotropin level with normal T_4 and free thyroxine (FT_4) levels, and lack of signs or symptoms of hypothyroidism.

HYPOTHYROIDISM IN THE NEONATAL PERIOD

Epidemiology

CH is the most common congenital endocrine disorder and the most common preventable cause of intellectual disability. Before the implementation of newborn screenings, the incidence of CH was approximately 1 in 7,000 live births. After the advent of newborn screenings in the mid-1970s, the incidence increased to 1 in 4,000 live births. The incidence appears to have continued increasing during the past few decades, in part due to changing demographics in developed countries and the lowering of the thyrotropin cutoff values by newborn screening programs which has increased the diagnosis of milder cases. The most recently reported incidence of CH in the general population of North America is approximately 1 in 2,500 live births, with wide variation according to geographic location and ethnic background. In 2008, a workshop of epidemiological experts evaluating the incidence of CH by race/ethnicity in California among infants born between 2001 and 2007 reported the incidences as 1 in 1,200 live births among Asian Indians, 1 in 1,600 live births among Hispanics, 1 in 2,380 live births among Asians, 1 in 3,533 live births among non-Hispanic whites, and 1 in 11,000 live births among non-Hispanic blacks. (1) Recent surveys of newborns from New York State and Massachusetts report incidences of 1 in 1,415 and 1 in 1,660 live births, respectively. (2) The increasing incidence of CH has also been documented in European populations and presently is as follows: British, 1 in 1,077; Greeks, 1 in 1,749; and Italians, 1 in 2,200. (2) There is a 2:1 female to male ratio in CH, secondary to thyroid dysgenesis. The risk of CH is higher among newborns with birth weights less than 2,000 g and greater than 4,500 g. Approximately 5% of newborns in the general population have a birth defect; the prevalence increases to approximately 10% in newborns with CH. Transient CH is more common among premature infants. Maternal hypothyroidism has been associated with transient hypothyroidism, and paternal hypothyroidism has been associated with CH.

Etiology

The most common cause of primary CH is abnormal development of the thyroid gland (dysgenesis), which corresponds to approximately 85% of cases. Approximately 66% of these cases are secondary to an ectopic location of the thyroid gland, followed by aplasia or hypoplasia of the gland. Most cases of thyroid dysgenesis or agenesis are sporadic and idiopathic. However, certain mutations in the genes encoding transcription factors involved in thyroid gland development have been reported in approximately 2% of these cases. (3) A defect in the normal production of thyroid hormones due to defects in enzymes and ion transporters, known as dyshormonogenesis, corresponds to approximately 10% to 15% of the cases of CH. These conditions are inherited in an autosomal recessive pattern.

Iatrogenic CH is seen in infants whose mothers received radioactive iodine after the 10th week of gestation. Therefore, any woman of childbearing age should have a pregnancy test performed before receiving diagnostic or therapeutic radioactive iodine. Central or secondary/tertiary hypothyroidism occurs in approximately 1 in 25,000 to 1 in 50,000 live births and is most commonly associated with other pituitary hormone deficiencies related to mutations in transcription factors associated with the development of the pituitary gland (see below). Transient CH is found in children whose mothers were treated with antithyroid medications during pregnancy. It is also seen in cases of excess or deficient maternal iodine intake, maternal thyrotropin-binding inhibitory immunoglobulin (TBII), or heterozygous mutations of *THOX2* or *DUOXA2*. Children with large congenital hepatic hemangiomas due to increased type 3 deiodinase activity may also have transient CH. (3)

In the preterm infant, the surge of thyrotropin, T_4, and T_3 is attenuated due to hypothalamic-pituitary-thyroid axis immaturity. Compared with full-term infants, these infants have lower levels of T_4. Levels of thyrotropin, FT_4, and T_3 are normal to

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low, and thyroglobulin levels are high in preterm infants because of an increased production of poorly iodinated thyroid hormone precursor. Low levels of thyroid-binding globulins (TBGs) contribute to the physiologic hypothyroxinemia of prematurity, which worsens according to the infant's degree of prematurity. In sick premature infants, this hypothyroxinemia may also be related to sick euthyroid syndrome, also known as nonthyroidal illness syndrome (discussed later). Male newborns with TBG deficiency have low levels of T_4 and T_3 and normal levels of FT_4, free triiodothyronine (FT_3), and thyrotropin. Newborns with low levels of albumin have similar, though milder, laboratory findings (discussed later). A diagram that summarizes the pathogenesis of hypothyroidism is presented in the Figure. The most common causes of CH are presented in Table 1.

Signs and Symptoms

Most newborns with CH do not have detectable clinical manifestations at birth due to the transplacental passage of maternal thyroid hormones. Further, most of these newborns have some thyroid function, unless they have thyroid agenesis. Even among infants with thyroid agenesis, the placental passage of T_4 and the lack of specific signs and symptoms of hypothyroidism make clinical diagnosis difficult. When early clinical findings are in fact present, usually it is among neonates with thyroid agenesis or total absence of thyroid hormone production and maternal hypothyroidism. Those infants whose mothers had normal thyroid hormone production may have only mild signs or symptoms during the neonatal period that become increasingly evident thereafter. Signs and symptoms of CH are presented in Table 2.

Diagnostic Evaluation

Newborn screening. Worldwide, approximately 25% of children are born in countries with newborn screening programs. In these countries, almost all infants with CH are diagnosed in the neonatal period. Newborn thyroid screening samples are collected from a heel-prick blood specimen on a filter paper between the second and fifth days after birth. Some programs obtain a second sample between the second and sixth weeks of age or upon hospital discharge if the infant has been admitted to a neonatal intensive care unit. Some newborns who are discharged from the hospital on the first day after birth have the sample taken at this time. The filter paper is mailed to a centralized laboratory. Each program has its own parameters for test results. Most programs in the United States evaluate thyrotropin levels, and measure T_4 only if the thyrotropin level is higher than their cutoff. Other programs evaluate T_4 with a reflex thyrotropin test in newborns with a T_4 level below the laboratory cutoff. Some programs routinely test both thyrotropin and T_4. In general, if the T_4 level is below the 10th percentile and/or the thyrotropin level is greater than 30 mIU/L, the designated physician is immediately contacted to arrange further evaluation and treatment. Some programs that use lower thyrotropin cutoff values identify more cases of mild hypothyroidism, but also generate more false-positive results. If the T_4 level is low and the thyrotropin level is normal, or if the T_4 level is normal and the thyrotropin level is slightly elevated but less than 40 mIU/L, some programs may recommend a repeat filter paper sample. The main disadvantage of programs that use only thyrotropin is the inability to detect cases of central hypothyroidism. False-positive

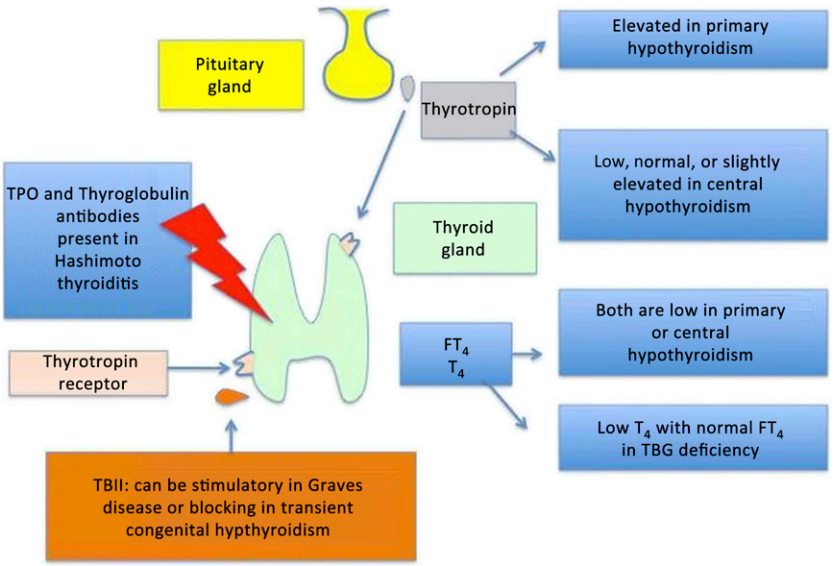

Figure. Pathogenesis of hypothyroidism. FT_4=free thyroxine; LT_4=levothyroxine; T_4=total thyroxine; TBII=thyrotropin-binding inhibitory immunoglobulins; TPO=thyroid peroxidase.

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TABLE 1. Causes of Congenital Hypothyroidism

Primary CH
Thyroid dysgenesis
Aplasia
Hypoplasia
Ectopic gland
Thyroid dyshormonogenesis
Sodium-iodine symporter (trapping) defect
Thyroid peroxidase defect
Thyroglobulin defect
Deiodinase defect
Resistant to thyrotropin binding or signaling
Thyrotropin receptor defect
G protein defect
Iatrogenic
Radioactive iodine given to the pregnant mother after 8 weeks of gestation
Secondary (central) hypothyroidism (see Table 7)
Peripheral CH
Thyroid hormone transport defect (monocarboxylate transporter 8)
Thyroid hormone metabolism defect (selenocysteine insertion sequence-binding protein 2)
Thyroid hormone resistance
Transient CH
Maternal or neonatal excess iodine exposure
Maternal or neonatal iodine deficiency
Maternal antithyroid drugs
Maternal thyrotropin receptor binding inhibitory immunoglobulin
Heterozygous *THOX2* or *DUOXA2* mutations
Congenital hepatic hemangiomas

TABLE 2. Signs and Symptoms of Congenital Hypothyroidism

Early findings
Macrosomia
Decreased activity
Large anterior fontanelle
Edema of the eyelids, hands, and feet
Prolonged jaundice
Hypotonia
Coarse facial features
Hypothermia
Pallor
Goiter
Protuberant abdomen
Late findings (after the neonatal period)
Poor sucking effort
Developmental delay
Decreased activity and lethargy
Poor growth
Umbilical hernia
Mottled, cool, and dry skin
Difficult breathing
Macroglossia
Generalized swelling (myxedema)
Hoarse cry

elevations in thyrotropin levels may be found when a sample was collected within the first 48 hours after birth. Among these infants, repeating the newborn screening at 2 weeks after birth is recommended. False-negative results may be found in critically ill infants or after blood transfusion. The most common causes of hypothyroidism and corresponding laboratory test findings are presented in Table 3.

Confirmatory testing. Newborns with abnormal thyroid screening test results should be referred immediately for evaluation and confirmatory testing. A blood specimen for thyrotropin and FT_4 measurement should be obtained. If T_4 is ordered instead of FT_4, TBG should be evaluated or a T_3 resin uptake test should be performed to avoid missing cases of TBG deficiency. In this condition (discussed below), the TBG level is low and T_3 resin uptake is elevated. The T_3 resin uptake is an indirect measure of the binding capacity of TBG. In this test, T_3 resin binder is mixed with serum from the patient and a trace amount of iodine 125–labeled T_3 is added. If the patient has low levels of TBG, the TBG would be saturated; therefore, a higher fraction of iodine 125–labeled T_3 binds to the resin. Thyrotropin values after the first week after birth should be less than 10 mIU/L. Primary hypothyroidism is confirmed if the infant has an elevated thyrotropin level with a low FT_4 level. Some preterm and/or newborns with low birth weights have low T_4 levels and normal thyrotropin levels. Their T_4 level usually normalizes by the sixth week after birth. If their T_4 and/or FT_4 level is

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very low and/or continues to be low after the sixth week after birth, the diagnosis of central hypothyroidism is likely. Some acutely ill infants have low levels of T_4 and FT_4 as part of sick euthyroid syndrome. This diagnosis is confirmed with a detection of an elevated reverse T_3 (rT_3) level. Some authors recommend evaluation of FT_4 by the equilibrium dialysis method when the FT_4 level is borderline abnormal or does not correspond to clinical manifestations. In the equilibrium dialysis method, patient serum is dialyzed against a buffer for 16 to 18 hours, separating FT_4 molecules from the protein-bound T_4 molecules. FT_4 molecules are able to cross the dialysis membrane because they are small and can be measured without being affected by TBG concentrations or thyroid autoantibodies. However, this test is time-consuming and expensive. Approximately 30% of children with a positive newborn screening result have definitive CH (elevated thyrotropin level with low FT_4 level).

Further imaging and laboratory evaluation may be performed to clarify the origin of thyroid disorder. A thyroid scan is the best test to determine the size and location of the thyroid gland. It can be performed within the first days of therapy, and a serum thyrotropin level should be measured at the time of the scan. In newborns, this test should be performed with iodine 123 or sodium pertechnetate Tc 99m. Absent radioactive isotope uptake is seen in thyroid aplasia, maternal TBII, thyrotropin β-mutations, thyrotropin receptor–inactivating mutations, and iodide-trapping defects. In cases of absent uptake, ultrasonography of the thyroid should be performed to determine whether the thyroid gland is present. An enlarged gland with increased uptake is seen in infants with dyshormonogenesis. In these cases, a perchlorate discharge and/or genetic tests are helpful to establish the diagnosis. Ultrasonography of the thyroid may also be ordered as the initial test; however, it is not as accurate as a scan in identifying ectopic glands. Infants with absent uptake on scan, a normal or small thyroid gland by ultrasonography, or a maternal history of autoimmune thyroid disease should have TBII measured. CH due to the presence of TBII antibodies, which block the thyrotropin receptor, is transient, lasting from a few weeks to 6 months after birth.

Insufficient or excessive iodine intake or exposure can produce hypothyroidism or hyperthyroidism. In infants with CH, born in areas of endemic iodine deficiency, measurement of urinary iodine will confirm low iodine levels. If there is a history of maternal excessive iodine ingestion or neonatal exposure to iodine, urinary iodine determination will confirm this diagnosis. The normal urinary iodine range in a neonate is approximately 50 to 100 μg/24 hours (nmol/24 hours). (3) Normal thyroid function test values according to age are presented in Table 4.

TABLE 3. Causes of Hypothyroidism and Laboratory Findings

Primary hypothyroidism (eg, dysgenesis, agenesis, dyshormonogenesis, and Hashimoto thyroiditis)	Elevated thyrotropin level with low T_4 and FT_4 levels; positive TPO and/or thyroglobulin antibody test results
Subclinical hypothyroidism	Slightly elevated thyrotropin level with normal T_4 and FT_4 levels
TBG deficiency	Normal thyrotropin level with low T_4 level, normal FT_4 level, and low TBG levels
Central hypothyroidism	Low, normal, or slightly elevated thyrotropin levels with low T_4 and/or FT_4 levels
Mild sick euthyroid syndrome	Normal thyrotropin level, low T_3 level, elevated rT_3 level, normal T_4 and FT_4 levels
Moderate sick euthyroid syndrome	Normal thyrotropin level, low T_3 level, elevated rT_3 level, low T_4 and FT_4 levels
Severe sick euthyroid syndrome	Low thyrotropin level, low T_3 level, elevated rT_3 level, low T_4 level, and low FT_4 level
Resistance to thyroid hormone	Normal or slightly elevated thyrotropin level with elevated T_4, T_3, FT_4, and FT_3 levels

FT_3=free triiodothyronine; FT_4=free thyroxine; rT_3=reverse triiodothyronine; T_3=total triiodothyronine; T_4=total thyroxine; TBG=thyroid-binding globulin; TPO=thyroid peroxidase.

Treatment

Because of the known correlation between the intelligence quotient (IQ) and the timing of thyroid hormone replacement initiation, treatment with levothyroxine (LT_4) should be started as soon as a diagnostic evaluation confirms the diagnosis of CH. If the thyrotropin level is greater than 40 mIU/L and the T_4 level is low, LT_4 should be started immediately after confirmatory samples have been taken, without waiting for results.

The initial recommended dose of LT_4 for infants with CH is 10 to 15 μg/kg daily. In the United States, only tablet formulations are approved for treatment; thus, the tablet should be crushed and mixed with water, breast milk, or formula. Thyrotropin, FT_4, and T_4 should be evaluated at 2 and 4 weeks after the initiation of LT_4 treatment. Thereafter, thyroid function levels should be measured every 1 to 2 months for the first 6 months after birth, every 2 to 3 months between age 6 months and 3 years, and every 6 to 12 months

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TABLE 4. **Normal Thyroid Function Values in Infancy and Childhood**[a]

AGE	T_4, μG/DL (NMOL/L)	FT_4, NG/DL (PMOL/L)	T_3, NG/DL (NMOL/L)	RT_3, NG/DL (NMOL/L)	TBG, μG/ML (NMOL/L)	THYROTROPIN, MIU/L
Premature Infants						
26–32 weeks (day 3–4)	2.6–14.0 (44–239)		24–132 (0.37–2.03)			0.8–6.9
Full-term infants						
Newborns		0.94–4.4 (12–57)[b]		90–250 (1.39–3.85)	19.2–44.7 (328–764)[b]	25–160 at 30 minutes after birth
1–3 Days	8.2–19.9 (140–340)		89–405 (1.37–6.24)			1.9–17.58[b]
Day 4						1.3–16
1 Week	6.0–15.9 (103–272)	0.95–4.0 (12–51)[b]	91–300 (1.40–4.62)	10–50 (0.15–0.77)	19.2–44.7 (328–764)[b]	0.58–5.58[b]
1–11 Months		0.65–1.9 (8–24)	85–250 (1.31–3.85)	10–50 (0.15–0.77)		0.9–7.7
Prepubertal children		0.65–1.9 (8–24)	119–218 (1.83–3.36)	10–50 (0.15–0.77)	12.7–27.9 (217–477)	0.6–5.5
1–2 Years	6.8–13.5 (116–231)					
3–10 Years	5.5–12.8 (94–219)					
Pubertal children	4.9–13.0 (84–222)	0.8–1.7 (10–22)	80–185 (1.23–2.85)	10–50 (0.15–0.77)	12.7–27.9 (217–477)	0.5–4.8

FT_4=free thyroxine; T_3=total triiodothyronine; T_4=total thyroxine; TBG=thyroid-binding globulin; rT_3=reverse triiodothyronine.
[a]*Data are ranges ± 2 SDS from mean values. Data are from the Endocrine Sciences Laboratory (2011) and Lem et al.* J Clin Endocrinol Metab. *2012;97 (9):3170–3278.*
[b]*FT_4 and thyrotropin were determined by chemiluminescence assays. TBG was measured by immunometric assay.*

thereafter. Evaluation of thyroid function 4 weeks after a change in LT_4 dosage is also recommended. The target range for FT_4 should be in the upper half of the laboratory reference range for age. The T_4 level should be between 10 and 16 μg/dL (171–273 nmol/L) for the first 2 years after birth; thereafter, levels should be on the upper half of the reference range for age. Maintaining TSH levels to below 5 mIU/L, ideally between 0.5 and 2 mIU/L, is recommended; however, some infants with CH have a certain degree of thyroid hormone resistance, and their thyrotropin level is not easily maintained within the recommended values without increasing levels of T_4 and FT_4 above the upper limits. In these cases and among infants with central hypothyroidism, when thyrotropin levels cannot be determined, monitoring should be based on T_4 and FT_4 levels. Because of the lack of bioequivalence among different brands of LT_4, it is not recommended to substitute different LT_4 formulations, particularly in cases of severe CH during the first 3 years after birth. If no signs of permanent hypothyroidism are obvious and the child has a eutopic thyroid gland, discontinuation of LT_4 for 30 days, with subsequent thyrotropin and FT_4 measurement, is recommended after age 3 years. If the levels are within the reference range, the diagnosis of transient hypothyroidism can be made; otherwise, treatment should be resumed. Children with a history of transient hypothyroidism should be carefully followed up for clinical symptoms, and thyroid tests should be performed if recurrence is suspected. Approximately one third of children with CH and eutopic thyroid gland will need to continue LT_4 treatment after reevaluation.

Delayed initiation of LT_4 treatment and persistent suboptimal levels of T_4 during the first year after birth have been associated with lower IQ attainment. A recent longitudinal, population-based cohort study found that young adults diagnosed with CH by neonatal screening reported a modest but significant increase in chronic diseases, visual problems, overweight, lower socioeconomic status, and lower full-time employment than their peers. The same study found an almost fourfold increase in hearing impairment among the CH group. (4) Hearing problems secondary to CH are persistent despite early diagnosis. Decreased health-related quality of life, primarily due to lower cognitive functioning, has been reported in patients with a history of CH. Because of the higher risk of congenital anomalies among infants with CH, careful physical examination and hearing tests should be performed. A summary of the treatment, monitoring, and thyroid function test targets are presented in Table 5.

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TABLE 5. Treatment, Monitoring, and Thyroid Function Test Targets

CONDITION	DOSE OF LT_4	FREQUENCY OF THYROID FUNCTION TESTS	TARGET THYROTROPIN	TARGET T_4	TARGET FT_4
Congenital hypothyroidism	10–15 μg/kg daily	2–4 Weeks after starting treatment. Every 1–2 months for first 6 months after birth Every 2–3 months between 6 months and 3 years after birth Then every 6–12 months	Less than 5 mU/L, ideally between 0.5 and 2 mU/L	10–16 μg/dL	Upper half of laboratory reference range
Acquired primary hypothyroidism	1–5 years 4–6 μg/kg daily 6–10 years 3–4 μg/kg daily >11 years 2–3 μg/kg daily	Repeat thyroid function tests 6 to 8 weeks after LT_4 treatment is initiated or the dose is modified, then every 6 to 12 months in children older than 3 years	Between 1 and 3 mU/L	Within reference range	Within reference range
Central hypothyroidism	Same as in congenital hypothyroidism if diagnosed in infancy and same as in acquired primary hypothyroidism if diagnosed later	Same as in congenital hypothyroidism if diagnosed in infancy and same as in acquired primary hypothyroidism if diagnosed later	If evaluated, thyrotropin should be suppressed; if unsuppressed, indicates undertreatment	Within reference range	Middle and upper parts of the reference range

FT_4=free thyroxine; LT_4=levothyroxine; T_4=thyroxine.

ACQUIRED PRIMARY HYPOTHYROIDISM: HASHIMOTO (AUTOIMMUNE) THYROIDITIS

Epidemiology

HT is the most common autoimmune disorder and the most common cause of hypothyroidism in children and adults. In pediatrics, most cases of HT are diagnosed during adolescence; however, it can present at any age, usually after the first year after birth. The prevalence of HT varies according to sex, ethnicity, and geographic location. The presence of positive antithyroid antibodies in the general population increases with age, from 5% to 10% among young adults to 10% to 20% among older adults. Women have 2 to 4 times the prevalence of antithyroid antibodies compared to men. Whites are affected more than Mexican Americans, while African Americans have the lowest prevalence. Iodine-deficient populations appear to have a lower incidence of HT and hypothyroidism. (5) HT is more commonly found in children with other autoimmune disorders or syndromes, especially Down syndrome, Turner syndrome, Noonan syndrome, type 1 diabetes mellitus (T1DM), and celiac disease. A list of the autoimmune syndromes that may include HT is presented in Table 6.

Etiology

Several factors are involved in the pathogenesis of HT, such as infiltrating lymphocytes, cell expression of major histocompatibility complex class II, Fas-mediated apoptosis, and cytokine release. Approximately 70% of the individuals with this condition have a genetic predisposition. As many as 20 to 60 immunosusceptibility genes have been associated with HT. The disease is then ultimately triggered by environmental factors. (6) The pathogenesis of HT is caused by infiltration of the thyroid gland by T_H1 and T_H2 cells. T_H1 cells regulate cell-mediated responses, which produce the principal damage to the gland. T_H2 cells regulate B lymphocytes, which are involved in antibody production. Numerous cytokines, complement, and other mediators produce damage to the thyrocytes, leading to cell death by apoptosis. Two main types of antibodies found in patients with HT are directed against thyroid peroxidase and thyroglobulin. These antithyroid antibodies do not appear to be important in the pathogenesis of HT. Pregnancy and environmental factors, such as infections, certain drugs (eg, lithium, amiodarone, interferon alfa, and hormone replacements, including estrogen), excess intake of iodine, stress, smoking, and toxins, are all considered triggers of the disease. Goiter formation results from cellular infiltration and thyroid follicular cell proliferation secondary to

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TABLE 6. **Autoimmune Syndromes That May Include Hashimoto Thyroiditis**

Autoimmune polyglandular syndrome, type 1
Candidiasis
Hypoparathyroidism
Addison disease
Autoimmune polyglandular syndrome, type 2
Addison disease
Hashimoto thyroiditis
Type 1 diabetes mellitus
Primary hypogonadism
Myasthenia gravis
Celiac disease
Immunodysregulation polyendocrinopathy X-linked syndrome
Early-onset type 1 diabetes mellitus
Colitis

thyrotropin elevation in response to decreased thyroid hormone production.

Symptoms and Signs

Approximately 80% of children and adolescents with HT are asymptomatic at the time of diagnosis. A goiter is present in approximately 70% of children with HT and is often the first manifestation of the condition. Children with moderate or severe hypothyroidism are often detected on evaluation of poor growth velocity, decreased energy, declining school performance, constipation, and/or dry skin. Some girls with severe hypothyroidism may present with precocious puberty and hyperprolactinemia, a condition known as the Van-Wyk-Grumbach syndrome. Some children with prolonged hypothyroidism develop dyslipidemia.

Some children with HT may present with clinical or subclinical hyperthyroidism caused by the release of stored thyroid hormone from the affected thyroid gland. The absence of ophthalmologic findings on physical examination and negative thyrotropin receptor–stimulating antibodies or negative TBII test results help to differentiate this condition from Graves disease, although both conditions may coexist in the same patient, and occasionally signs and symptoms can alternate between one condition and the other. Hyperthyroidism secondary to HT is called Hashitoxicosis.

On physical examination of patients with HT, the thyroid gland is diffusely enlarged and has a rubbery consistency. The surface is described as pebbly or bosselated. A lymph node over the isthmus, called a Delphian node, may be palpated.

Diagnostic Evaluation

The initial laboratory evaluation of a child with suspected hypothyroidism should include serum thyrotropin and FT_4 levels. A low FT_4 value is diagnostic of hypothyroidism, and an elevated thyrotropin level is diagnostic for primary hypothyroidism. If the thyrotropin level is low, normal, or slightly elevated in the presence of a low FT_4 level, the likely diagnosis is central hypothyroidism. Measurement of T_4 may help to clarify cases with borderline low or high FT_4 levels; however, measurement of T_4 instead of FT_4 can be misguiding. The level of T_4 depends on the level of TBG and other proteins and/or the amount of T_4 bound to them. For example, children with TBG deficiency or those taking certain medications, (eg anticonvulsants, including phenytoin and carbamazepine) that compete with T_4 to bind TBG, have lower levels of T_4. Adolescent girls treated with birth control pills have elevated T_4 levels due to increased TBG levels secondary to estrogens. If the levels of FT_4 are inconsistent with the patient's clinical presentation, FT_4 by dialysis should be ordered.

Presence of thyroid peroxidase and/or thyroglobulin antibodies confirms the diagnosis of HT. Ultrasonography of the thyroid is recommended when a thyroid nodule is palpable or when the child has a large goiter in which there may be a nodule that is not easy to palpate. The thyroid gland in patients with HT is commonly reported as enlarged, with heterogeneous echogenicity.

At presentation, thyroid function of children with HT is characterized by euthyroidism in 35% to 50% of cases, subclinical hypothyroidism in 20% to 35% of cases, hypothyroidism in 20% of cases, subclinical hyperthyroidism in 3% to 8% of cases, and hyperthyroidism in 3% to 6% of cases.

MANAGEMENT

Children at high risk of hypothyroidism due to HT, such as those with T1DM, Down syndrome, or Turner syndrome, should undergo a routine evaluation of their thyrotropin levels as part of their annual visit. Children with HT without hypothyroidism should have their thyrotropin levels evaluated every 6 to 12 months. Children with HT and subclinical hypothyroidism without treatment with LT_4 should have their thyrotropin and FT_4 levels monitored every 6 months.

LT_4 should be first-line treatment for children with hypothyroidism. The dose varies according to age and severity of hypothyroidism. In children, dosing according

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to age is typically as follows: ages 1 to 5 years, 4 to 6 μg/kg daily; ages 6 to 10 years, 3 to 4 μg/kg daily; and 11 years and older, 2 to 3 μg/kg daily. Children with mild hypothyroidism may be prescribed a lower dose of LT_4. Some experts recommend starting a low dose of LT_4 with progressive increases over a few weeks when a child has severe hypothyroidism because some of these children develop adverse effects, such as headaches, insomnia, hyperactivity, and attention deficit, when given a full dose. For children with a large goiter, some endocrinologists aim to maintain a thyrotropin level below 1 mIU/L with the purpose of decreasing the goitrogenic effect of thyrotropin. Once a patient begins LT_4 or a dose has been modified, thyrotropin and FT_4 levels should be measured 6 to 8 weeks later. When the thyrotropin level is within the recommended range of 1 to 3 mIU/L, thyroid function test results should be monitored every 6 to 12 months in children older than 3 years.

Traditionally, LT_4 was to be taken on an empty stomach at least 30 minutes before breakfast; however, this medication can be taken with foods that do not affect its absorption. Foods high in fiber, soy-containing foods or formulas, and medications such as iron and calcium are known to affect LT_4 absorption. Children with intestinal malabsorption secondary to inflammatory bowel disease and celiac disease may require higher doses of LT_4. Because of the long half-life of LT_4, the dose may be doubled the following day in the case of missing one dose.

The Drug and Therapeutic Committee of the Pediatric Endocrine Society recommends consistency in medication administration and thyroid function monitoring. Even though the absorption of LT_4 on an empty stomach may be better than with or after meals, the most important factor in treating hypothyroidism is regularity in medication dosing and thyroid hormone testing, with subsequent appropriate dose adjustment.

Long-term Prognosis in Children With HT

Between 50% and 80% of children with HT, who are euthyroid or have subclinical hypothyroidism at presentation, remain euthyroid 5 years later. The presence of a goiter, Down syndrome, Turner syndrome, and/or elevated levels of antithyroid antibodies increases the risk of developing hypothyroidism in the future. Some studies of adults with positive antithyroid antibody test results have shown that approximately 45% of these adults test negative for antibodies over time, particularly those with lower baseline antibody levels. In adults who test positive for antithyroid antibodies, the chance of progression to hypothyroidism is between 1% and 6.5% per year. This is positively correlated with baseline thyrotropin levels. (5)

Most children with HT presenting with hyperthyroidism (Hashitoxicosis) will have resolution of this condition less than a year after diagnosis. A small percentage of children and adolescents with HT may later develop Graves disease.

Although some authors have reported an association between HT and papillary thyroid carcinoma, population-based fine-needle aspiration studies have not found a statistically significant correlation between these conditions. Thyroidectomy studies that reported statistically significant positive correlations were subject to selection bias. (7)

Some authors have described patients with idiopathic encephalopathy and positive antithyroid antibody test results who respond well to corticosteroid therapy. This condition was referred to as Hashimoto encephalopathy or corticosteroid-responsive encephalopathy associated with autoimmune thyroiditis. Because of the lack of evidence that these antibodies have any action in the central nervous system and because there is no correlation between the level of antibodies and severity of neurologic manifestations, it is not possible to determine whether HT causes this type of encephalopathy.

OTHER CAUSES OF ACQUIRED PRIMARY HYPOTHYROIDISM

Sick Euthyroid Syndrome

Sick euthyroid syndrome, also known as nonthyroidal illness, refers to changes in thyroid function tests observed in a variety of acute or chronic illnesses among individuals without a history of thyroid disease. The first thyroid function test changes noted in these patients is a decrease in T_3, with increased rT_3 levels. In patients with more severe illnesses, T_4 and FT_4 levels are also low. Thyrotropin levels may also be low in patients with severe illnesses due to hypothalamic-pituitary axis dysfunction. A direct correlation between low T_4 levels and poor clinical outcomes has been reported among critically ill patients. Low levels of thyrotropin, T_4, and T_3 are associated with high mortality. Sick euthyroid syndrome is commonly seen among children with diabetic ketoacidosis.

Sick euthyroid syndrome results from an alteration in the activity of deiodinase enzymes, with a decrease in type 1 enzymes and increases in types 2 and 3. Poor caloric intake inhibits type 1 deiodinase, decreasing T_3 levels and increasing rT_3 levels. This appears to be a mechanism to preserve body protein stores in increased catabolic states observed in sick individuals. Treatment of critically ill patients with severe hypothyroxinemia has not proven to be beneficial. Most studies concerning the treatment of patients with sick euthyroid syndrome, including premature neonates, have not definitively demonstrated positive or negative effects of thyroid hormone replacement therapy.

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Iodine Deficiency

HT is by far the most common cause of primary hypothyroidism in children and adolescents in iodine-sufficient areas. Worldwide, iodine deficiency affects approximately 2 billion people and is the leading preventable cause of intellectual disability. However, it is rare in North America and other countries with routine, widespread salt iodization. The Food and Drug Administration recommends an intake of 150 μg of iodine daily.

Hypothyroidism Secondary to Medications

Thionamides, such as methimazole, carbimazole, and propylthiouracil, are used to treat hyperthyroidism. Propylthiouracil is no longer recommended for treatment in children or adolescents because of the risk of liver failure. Thionamides can produce hypothyroidism when used in high doses or for a prolonged period of time without close monitoring of thyroid function. Lithium, used to treat mood disorders, may also produce hypothyroidism in some patients. Usually, it is mild and does not require medical treatment. Amiodarone is an antiarrhythmic medication that contains a high concentration of iodine. This medication may produce inhibition of organification in the thyroid gland, with a subsequent decrease in the formation and release of T_4 and T_3 (Wolff-Chaikoff effect); it also decreases the conversion of T_4 to T_3, with a subsequent increase in thyrotropin levels. Amiodarone-induced hypothyroidism may affect up to 15% of patients taking the medication; however, it is often transient and resolves soon after discontinuation of use. Excessive use of iodinated antiseptics in newborns and infants can also produce hypothyroidism.

Thyroid or Neck Radiation or Surgery

Some children or adolescents with hyperthyroidism secondary to Graves disease or autonomous hyperfunction of the thyroid gland, such as seen in McCune-Albright syndrome, are unable to tolerate therapy with thionamides because of their adverse effects. These children and those without medication adherence may be treated with radioactive iodine or thyroidectomy. Subsequently, most will develop permanent hypothyroidism.

Subclinical Hypothyroidism

Subclinical hypothyroidism is defined by a thyrotropin level above the upper limit of the laboratory reference range, with FT_4 within the reference range. In the pediatric population, its prevalence is slightly below 2%. This condition is diagnosed on routine evaluation of thyroid function test results or as part of the evaluation of children with goiters, signs or symptoms of thyroid disease, a family history of thyroid disease, or conditions carrying a high risk for HT.

Most children with subclinical hypothyroidism revert to euthyroidism or remain with subclinical hypothyroidism. Only a few progress toward overt hypothyroidism. The presence of goiter, antithyroid antibodies, or increasing thyrotropin levels increases the risk of developing overt hypothyroidism. Treatment with LT_4 is not recommended in children with thyrotropin levels below 10 mIU/L, without a goiter, and with negative antithyroid antibody test results. Treatment with LT_4 should be considered among children with subclinical hypothyroidism and a large goiter, subclinical hypothyroidism associated with chronic conditions such as T1DM, thyrotropin levels above 10 mIU/L, or signs or symptoms of hypothyroidism. (8)

Children with obesity have higher levels of thyrotropin and FT_3 compared with healthy weight children. They have a higher prevalence of subclinical hypothyroidism that is not secondary to iodine deficiency or HT. Thyrotropin elevation among obese individuals appears to be mediated by high levels of leptin and is reversible after substantial weight loss. However, the 1946 British Cohort study found that childhood obesity increased susceptibility to hypothyroidism and HT between the ages of 60 and 64 years, especially among women. (9)

An increased prevalence of subclinical hypothyroidism has been reported among children fed with soy-based milk formulas and among those taking certain medications, including antiretrovirals, interferon, and anticonvulsant medications, such as carbamazepine, sodium valproate, and gabapentin.

Central or Secondary/Tertiary Hypothyroidism

Central hypothyroidism is caused by insufficient thyrotropin stimulation of a normal thyroid gland due to a disorder of the hypothalamus or pituitary gland. The prevalence of this condition has been estimated to be between 1 in 20,000 to 1 in 80,000 in the general population. (10) When milder forms of this condition have been included, its incidence in neonates has been found to be as high as 1 in 16,000. The prevalence of central hypothyroidism does not differ by sex. The most common causes of central hypothyroidism are combined pituitary hormone deficiencies, which may be genetic or secondary to hypothalamic and/or pituitary neoplasias or trauma. Isolated central hypothyroidism is rare (see Table 7 for causes of central hypothyroidism). The diagnosis is made when FT_4 levels are low and thyrotropin levels are normal, low, or slightly elevated. Therefore, clinicians or newborn screening programs that only evaluate thyrotropin levels may miss the diagnosis of central hypothyroidism.

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TBG ANOMALIES

Only 0.3% of T_3 and 0.03% of T_4 in the circulation are free. Thyroid hormones in plasma are bound to TBG (70%–80%), transthyretin (10%–15%), and albumin (10%–15%). TBG deficiency is an X-linked condition that affects 1 in 4,000 to 1 in 10,000 newborn males and is often confused with central hypothyroidism. Affected infants have low levels of T_4 and T_3 and normal thyrotropin levels. The diagnosis is confirmed by measuring FT_4 and FT_3 and/or TBG levels. Some females who are carriers have borderline low or mildly decreased levels of T_4 levels. Decreased TBG levels are also observed in patients who have been treated with androgens or high doses of corticosteroids, patients with excess growth hormone production, or those with nephrotic syndrome. TBG levels are elevated, with subsequent elevation in T_4 and T_3 levels, in pregnant women, newborns and young infants, patients with porphyria or active hepatitis, and patients treated with estrogens.

RESISTANCE TO THYROID HORMONE

Resistance to thyroid hormone is characterized by decreased activity of thyroid hormones on their receptors. It is caused by heterozygous mutations in the gene encoding for the thyroid hormone receptor β and, as recently described, the thyroid hormone receptor α_1. Children with resistance to thyroid hormones have elevated circulating levels of FT_4 and FT_3 with unsuppressed thyrotropin that is not the result of central hyperthyroidism (pituitary adenomas). Their thyrotropin level is normal or slightly elevated. The resistance to thyroid hormones may be more prominent in peripheral tissues or in the hypothalamic-pituitary area. In the peripheral form, most tissues outside the hypothalamus and pituitary gland are involved. Affected individuals usually have a normal metabolism because of the compensatory effects of high levels of thyroid hormones. In the pituitary form, signs and symptoms of hyperthyroidism are present. The clinical manifestations depend of the severity of the hormonal resistance, which may be highly variable. Most individuals with this condition have a goiter and normal metabolism; however, some may have clinical evidence of thyroid hormone deficiency and thyroid excess in certain tissues. Some children may have delays in growth and bone age, with hyperactivity and tachycardia.

Infants and children with resistance to thyroid hormones should be treated when the thyrotropin level is elevated, the bone age is delayed, or the child presents with failure to thrive. In some individuals in whom the peripheral tissue resistance to thyroid hormones is higher than in the pituitary, treatment with higher doses of LT_4 may be indicated. If the patient's primary signs or symptoms are those of hyperthyroidism, symptomatic treatment with a β-blocking agent is recommended. Some children with thyroid hormone resistance have improvement of some of the signs or symptoms related to this condition when treated with LT_4; however, some may develop signs and/or symptoms of hypothyroidism when treated with this medication.

The outcome of these individuals is highly variable according to the distribution and degree of resistance to thyroid hormones. Older family members affected by the condition may serve as guides for the treatment and prognosis of affected youngsters. In most cases, the partial tissue resistance to thyroid hormone is properly compensated for by an increased endogenous production of thyroid hormones, and treatment is not needed.

TABLE 7. **Causes of Central Hypothyroidism**

Neoplastic lesions or defects of the hypothalamic-pituitary area
Craniopharyngiomas
Pituitary adenomas
Rathke cleft cysts
Empty sella
Cranial surgery or irradiation
Meningiomas
Injuries
Head trauma
Traumatic delivery
Genetic conditions
Combined pituitary hormone deficiencies (mutations on *POU1F1, PROP1, HESX1, LHX3, LHX4, LEPR*)
Isolated: thyrotropin β or thyrotropin receptor mutations
Autoimmune conditions
Lymphocytic hypophysitis
Polyglandular autoimmune syndromes
Infiltrative conditions
Sarcoidosis
Langerhans histiocytosis
Infections
Tuberculosis
Mycoses

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Summary

- On the basis of strong clinical evidence, congenital hypothyroidism should be identified and treated early to avoid potentially profound cognitive deficits. (3)
- On the basis of strong clinical evidence, the dose of levothyroxine is higher at early ages and progressively decreases into adulthood. (3)
- On the basis of observational studies and consensus, children with congenital hypothyroidism and a eutopic thyroid gland should discontinue levothyroxine treatment at age 3 years to determine whether their hypothyroidism was transient. (3)
- On the basis of observational studies, most patients with Hashimoto thyroiditis present with a goiter and without hypothyroidism. (6)
- On the basis of observational studies, subclinical hypothyroidism is more common among obese children. (8)
- On the basis of strong clinical evidence, children with central hypothyroidism should have other pituitary hormone deficiencies ruled out. (10)

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Parent Resources from the AAP at HealthyChildren.org

- English: http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Thyroid-Disorders-Treatment.aspx

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PIR Quiz

1. The state laboratory for newborn screening informs you that a newborn tested on the second day after birth has a total thyroxine (T_4) concentration of 11 μg/dL (188 nmol/L) (reference range, 8.2-19.9 μg/dL [140-340 nmol/L]) and a thyrotropin concentration of 22 mIU/L (reference range, 1.9-17.58 mU/L). The infant is now 4 days old and is doing well. Which of the following is the most appropriate course of action?
    A. Initiate treatment with levothyroxine (LT_4) and repeat the newborn screen immediately.
    B. Reassure the mother that no further testing is necessary.
    C. Remeasure T_4 and thyrotropin at age 2 weeks.
    D. Measure thyroid-binding globulin (TBG).
    E. Determine the ratio of triiodothyronine (T_3) to reverse triiodothyronine (rT_3).
2. The state laboratory for newborn screening informs you that a newborn who was tested on the second day after birth has a T_4 concentration of 7.5 μg/dL (128 nmol/L) (reference range, 8.2-19.9 [140-340 nmol/L]) μg/dL and a TSH concentration of 42 mIU/L (reference range, 1.9-17.58 mIU/L). The infant is now 4 days old and is doing well. Which of the following is the most appropriate course of action?
    A. Initiate treatment with LT_4 and repeat the newborn screen immediately.
    B. Reassure the mother that no further testing is necessary.
    C. Remeasure T_4 and thyrotropin at age 1 week and treat if results confirm hypothyroidism.
    D. Measure TBG.
    E. Determine the ratio of T_3 to rT_3.
3. Treatment with LT_4 for hypothyroidism was started at 4 days of age in an infant girl. The diagnosis of hypothyroidism was based on low T_4 and free thyroxine (FT_4) and elevated thyrotropin levels. The patient is now 1 year old. She is developing normally and has no clinical signs of hypothyroidism. Thyroid is in eutopic position. The laboratory monitoring has found desired concentrations of T_4, FT_4, and thyrotropin. Which of the following statements is most correct?
    A. Discontinue treatment if FT_4 concentrations are normal by the more reliable equilibrium dialysis method.
    B. Discontinue treatment if the sodium pertechnetate Tc 99m scan result is normal to rule out dyshormonogenesis.
    C. Because this child most likely has transient hypothyroidism, discontinue LT_4 treatment for 1 month and measure her thyrotropin and FT_4 levels at regular intervals.
    D. Treatment with LT_4 should be lifelong because periodic depression of thyroid function has been reported in such patients.
    E. Wait until she is age 3 years and if the thyroid function study results remain normal, discontinue LT_4 treatment for 30 days with subsequent thyrotropin and FT_4 measurements.
4. A 13-year-old girl presents with decreased energy, declining school grades, and constipation for the last 9 months. Review of medical records indicates that she has gained 20 lb 2 years ago and that her height has decreased from being in the 95th percentile to the 50th percentile during this period. Examination reveals normal vital signs. Diffuse prominence of rubbery consistency is noted in the lower neck area anterior to sternocleidomastoid muscle. No other abnormalities are noted. Which of the following is the next best step in making the diagnosis?
    A. Measurement of antithyroid antibodies.
    B. Measurement of serum thyrotropin and FT_4.
    C. Measurement of serum TSH and T_3/rT_3 ratio.
    D. Sodium pertechnetate Tc 99m scan of the neck.
    E. Ultrasonography of the neck.

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5. The mother of a 1-year-old boy with Down syndrome is concerned about his thyroid function. A growth chart designed for boys with Down syndrome shows his weight is at the 25th percentile and length is below the third percentile. Serum FT_4 and thyrotropin concentrations are below normal. Determination of serum concentration of which of the following is most important at this time?

   A. Androgen and gonadotropin-releasing hormone.
   B. Cortisol and adrenocorticotropic hormone.
   C. Growth hormone and somatomedin C.
   D. Insulin and insulinlike growth factor 1.
   E. Parathyroid hormone and calcium.

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Hypothyroidism

Alejandro Diaz and Elizabeth G. Lipman Diaz

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pneumonic, although it belongs in a subset of causes of lactic acidosis.

Lactic acidosis is most commonly caused by cardiogenic shock, distributive shock, hypovolemia, or ingestion (eg, metformin). However, knowledge of the biochemical pathway that surrounds lactic acidosis reveals a much broader differential diagnosis, including mitochondrial disorders, cyanide poisoning (blocks electron transport chain), or any other process that interferes with aerobic metabolism, including thiamine deficiency. Given the current national shortage of IV multivitamins, thiamine deficiency should remain on the differential diagnosis for patients receiving long-term TPN.

Treatment

Thiamine deficiency should be treated with IV thiamine, which is generally safe and well tolerated. We gave our patient 400 mg of IV thiamine every 4 hours for several days, based on data that parenteral doses less than 200 mg may be ineffective in adults. We recommend consultation with a pediatric gastroenterologist and a pediatric pharmacist at your institution before dosing IV thiamine.

Lessons for the Clinician

- Signs and symptoms of thiamine deficiency may include encephalopathy, lactic acidosis, and cardiovascular collapse.
- Thiamine deficiency diagnosis should be based on the differential diagnosis for unexplained anion gap metabolic acidosis.
- It is important to recognize thiamine deficiency in patients receiving long-term TPN, particularly in the setting of a national multivitamin shortage.
- Early diagnosis of thiamine deficiency is essential for prevention of irreversible damage.

(Matthew B. Wallenstein, MD, Elizabeth B. Burgener, MD, Jenna Klotz, MD, John A. Kerner, MD, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA)

To view Suggested Reading lists for these cases, visit https://pedsinreview.aappublications.org and click on the "Index of Suspicion" link.

Correction

CME Question #2 for the August article "Hypothyroidism" (Diaz A. and Lipman Diaz, E. *Peds in Rev.* 2014;35(8):336, doi: 10.1542/pir.35-8-336) has an error in the vignette as printed. The term "thyroxine" should be "TSH." The sentence should read, "The state laboratory for newborn screening informs you that a newborn who was tested on the second day after birth has a T4 concentration of 7.5 μg/dL (128 nmol/L) (reference range, 8.2–19.9 μg/dL [140–340 nmol/L]) and a TSH concentration of 42 mIU/L (reference range, 1.9–17.58 mIU/L)." A correction has been posted online, and the entire quiz has been corrected online. The journal regrets the error.

ANSWER KEY FOR OCTOBER 2014 PEDIATRICS IN REVIEW:

Celiac Disease: 1. D; 2. C; 3. D; 4. A; 5. D.

Respiratory Distress in the Newborn: 1. A; 2. A; 3. E; 4. B; 5. C.

Evaluation and Treatment of Nonmonosymptomatic Enuresis: 1. C; 2. E; 3. E; 4. B; 5. E.

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