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The Laboratory Features of Congenital Hypothyroidism and Approach to Therapy

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Abstract

Congenital hypothyroidism (CH) is one of the most common preventable causes of intellectual disability. Thyroid hormone is required for normal brain development, but neonates with CH typically appear healthy at birth, which leads to delays in diagnosis and treatment. In developed countries, newborn screening programs have led to earlier diagnosis and treatment of CH, resulting in improved neurodevelopmental outcomes. Neonates with an abnormal newborn screen require prompt confirmatory serum thyroid function tests and treatment with thyroid hormone. Further evaluation for the etiology of CH should not delay treatment decisions.

INTRODUCTION

Congenital hypothyroidism (CH) refers to a group of disorders that result in decreased circulating biologically active thyroid hormone. The incidence of CH in iodine-sufficient areas is approximately 1 in 3,000 to 1 in 4,000 live births, with variation worldwide. (1) Evidence from newborn screening programs in the United States reports an incidence of 1 in 2,372 live births in 2002, increased from 1 in 4,097 in 1987. These programs have found that the incidence is higher in Hispanic and Asian neonates and lower in black neonates. (2)(3) The incidence is nearly 1.5–2:1 in female versus male neonates, and is also higher in twin births, older mothers, and preterm infants. (2)(3)(4)(5)(6) The reasons for this rise in overall incidence of CH is thought to be multifactorial and related to changes in the screening cutoffs resulting in increased detection of milder cases, increased screening of preterm infants, and increased birth of Hispanic and low-birth-weight infants. (1)(3)

The initial symptoms of CH are nonspecific because of the subtle features and protective effects of maternal hormone on the fetal brain. As the affected neonate ages, the degree of hypothyroidism worsens, increasing the risk of significant irreversible brain damage. Newborn screening, initially piloted in 1974, has resulted in earlier diagnosis and treatment of CH. Neonates with an abnormal newborn screening result should have confirmatory testing and begin levothyroxine (LT₄) treatment promptly to improve growth and neurodevelopmental outcomes. (7)

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THYROID PHYSIOLOGY

Thyroid hormone plays an important role in energy metabolism, control of body temperature, growth, bone formation, and the development of the central nervous system. Specifically, thyroid hormone acts on neuronal differentiation, synapsis development, and myelination in the prenatal and newborn periods, regulating neurodevelopment. (8) There are 2 active thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). Both T_4 and T_3 are secreted by the thyroid gland, though the majority of circulating T_3 is derived from peripheral tissue deiodination of T_4 . Deiodination of T_4 to T_3 is catalyzed by a group of enzymes known as iodothyronine deiodinases. Active thyroid hormone T_3 binds to the thyroid hormone receptors ($TR\alpha$ or $TR\beta$) and affects the expression of thyroid hormone–dependent genes.

The hypothalamic-pituitary-thyroid (HPT) axis works to maintain a stable concentration of thyroid hormone. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the thyrotropic cells of the pituitary to produce thyroid-stimulating hormone (TSH), also referred to as *thyrotropin*. TSH then stimulates the thyroid follicular cells to produce T_4 and T_3 . Hypofunctioning of the thyroid gland typically results in increases in TRH and TSH production, except in cases of pituitary or hypothalamic dysfunction (central hypothyroidism) and pituitary resistance to thyroid hormone feedback.

The fetal thyroid gland becomes visible at the fourth week of gestation and begins trapping iodine at 10 weeks' gestation. (9) In the first trimester, most of the active fetal thyroid hormone results from maternal thyroid hormone crossing the placenta. Maternal hypothyroidism alone during early gestation is a significant risk factor for impaired psychomotor development. (10) The fetal HPT axis becomes active at about 18 weeks' gestation and then functions independent of the pregnant woman, with negligible TSH placental transfer. (11) T_4 levels steadily rise after 18 weeks of gestation and T_3 levels rise after 30 weeks of gestation. In healthy term infants, there is a surge in TRH and TSH production shortly after birth, which has been attributed to cold exposure, leading to a rise in both T_4 and T_3 levels in the first 24 to 36 hours after birth. (12)(13) Figure 1 summarizes the changes in serum TSH and T_4 concentrations during the first 5 days of age.

ETIOLOGY OF CH

Most infants with CH are healthy at birth because of a small amount of placental transfer of maternal T_4 . In addition, intracerebral T_4 to T_3 conversion is increased, leading to availability of brain T_3 , despite low serum concentrations of T_4 . (11) T_4 has a half-life of 7 to 10 days, so the signs and symptoms of CH become more apparent as maternal T_4 is metabolized. However, when both maternal and fetal hypothyroidism are present, there are significant neurointellectual delays despite adequate diagnosis and treatment. This may occur in the setting of severe iodine deficiency or potent blocking TSH receptor antibodies (TRAbs). (10)

The American Academy of Pediatrics (AAP) guidelines from 2006 dictate that “infants with low T_4 and elevated TSH concentrations have CH until proven otherwise. All infants with

hypothyroidism, with or without goiter, should be rendered euthyroid as promptly as possible by replacement therapy with TH (thyroid hormone).” (14)

Neonates with primary CH have an elevated TSH, with low T₄, T₃, and free T₄ (FT₄) values. In iodine-sufficient areas, 95% of cases of CH are primary, meaning they result from abnormalities of the thyroid gland. Although some cases are transient, such as with the presence of TRAbs, treatment should be started until the underlying etiology disappears and should not be delayed for diagnosis. Thyroid dysgenesis, failure of the thyroid gland to appropriately develop, accounts for 85% of primary CH. (15) Thyroid ectopy is usually sporadic and accounts for two-thirds of the cases of thyroid dysgenesis. It is more common in females, with a lingual thyroid representing 90% of cases. Thyroid agenesis and thyroid hypoplasia cause the other one-third of cases of thyroid dysgenesis. (15)(16) Mutations have been reported in some transcription factor genes that regulate thyroid gland development, but a genetic mutation is only found in 2% to 5% of cases of thyroid dysgenesis. (17) Thyroid dyshormonogenesis, because of a defect in the enzymes or transporters involved in thyroid hormone production, accounts for up to 10% to 15% of cases and is typically inherited in an autosomal recessive pattern. (18) Mutations in the thyroid peroxidase gene are the most prevalent form of inherited CH. Other causes include defects in peripheral thyroid hormone transport, metabolism, or action. (16) Neonatal hyperthyrotropinemia occurs when patients have a normal T₄ and FT₄ and mildly elevated TSH. These newborns require close follow-up until their TSH value normalizes, but may not require treatment.

Neonates with central CH have a low-normal TSH with low T₄, T₃, and FT₄ values. Central hypothyroidism is caused by deficient TSH production in the setting of a normal thyroid gland. The incidence of central hypothyroidism is 1 in 25,000 to 50,000 live births. (15) Central hypothyroidism is more challenging to diagnose, because human chorionic gonadotropin stimulates the normal fetal thyroid gland and thyrotrope function is not completely absent in most cases. It can be caused by various disorders affecting the hypothalamus or pituitary gland. Genes leading to TSH deficiency can be isolated or result in multiple pituitary hormone deficiencies (such as deficiency of adrenocorticotropin, growth hormone, and gonadotropins). (19) If there are signs of multiple pituitary deficiencies (micropenis and undescended testicles from luteinizing hormone deficiency and hypoglycemia from cortisol and/or growth hormone deficiency) or midline facial defects, brain magnetic resonance imaging (MRI) should be performed to assess for an absent or hypoplastic pituitary gland or abnormalities in the pituitary stalk. Septo-optic dysplasia can manifest with CH and should be considered in the presence of pituitary deficiencies, visual defects and/or blindness, congenital nystagmus, and midline brain defects. Multiple pituitary abnormalities may reflect a genetic defect in pituitary formation, such as *PROPI*, *LHX3*, or *Pou1F1* mutations. (16) If isolated, central hypothyroidism typically results from a mutation in the beta subunit of the *TSH* gene or *TRH* receptor gene. (15) Brain trauma, asphyxia, and excessive treatment of maternal hyperthyroidism can also lead to central hypothyroidism. Neonates with central hypothyroidism may have similar laboratory values as neonates who are premature, critically ill, or have thyroxine-binding globulin (TBG) deficiency.

Preterm and critically ill infants have a smaller rise in TSH, T₄, T₃, and FT₄ at birth compared with healthy term infants, because of immaturity of the HPT axis and non-

thyroidal illness (sick euthyroid syndrome). The reference range for thyroid hormones varies by gestational and post-natal age. Preterm infants may also have lower concentrations of TBG. During the first week after birth, there is a decline in T_4 levels, which is greater in very-low-birthweight and more premature infants. Preterm or critically ill infants with low T_3 and T_4 levels and normal TSH levels on initial evaluation typically have normalization of the thyroid function by 6 to 10 weeks after birth without needing treatment. Van Wassenaeer et al showed that neonates who were treated with T_4 at less than 27 weeks' gestation had improvement in mental development scores at 2 years of age and motor development outcomes at 10.5 years of age; however, when T_4 was administered to neonates at 27 weeks' gestation or later, treated infants had worse neurodevelopmental outcomes than those who received a placebo. (20)(21) Currently, there is insufficient evidence to recommend treating preterm infants with abnormal thyroid function. However, preterm and critically ill infants require close monitoring because there may be a delay in the appropriate TSH elevation in cases of transient or permanent primary hypothyroidism, thus leading to a delay in diagnosis and treatment of CH. (22)

A low total T_4 with normal TSH and FT_4 levels in a healthy infant may indicate TBG deficiency. This is an X-linked disorder with an incidence of 1 in 4,000 males. There is no true deficiency, so treatment is not needed. (15) Rarely, a neonate may have primary hypothyroidism and TBG deficiency. In these cases, the TSH will be useful in determining the accurate diagnosis.

Transient hypothyroidism can be seen with maternal blocking TRAbs, exposure to maternal antithyroid medications, iodine deficiency or excess, and large congenital hepatic hemangiomas (increased type 3 deiodinase activity). (15) TRAbs, as seen in maternal Graves' disease, cross the placenta and can block or mimic the function of TSH. Neonatal Graves' disease (also called neonatal autoimmune hyperthyroidism) occurs in about 2% of neonates born to mothers with Graves' disease and may be associated with serious neonatal adverse events, including goiter, intrauterine growth restriction, oligohydramnios, prematurity, tachy-cardia and heart failure, hepatomegaly, and death. (23) Alternatively, hypothyroidism from maternal Graves' disease has an incidence of 1 in 180,000. The antibodies typically disappear from the serum of the affected infant by 3 to 5 months of age. (24)

In developing countries, iodine deficiency continues to be a significant cause of preventable cognitive deficits. Selenium and iron deficiencies may have an effect on neurologic development and thyroid response to iodine. (14) Iodine exposure with surgery and procedures can increase the risk of hypothyroidism secondary to iodine overload. This is usually transient but short-term therapy may be needed. (15)

Patients with Down syndrome have a mild increase in TSH concentration, with lower mean FT_4 values than the general population. Down syndrome is associated with higher rates of thyroid dysfunction, most commonly subclinical hypothyroidism and thyroid autoimmunity. The AAP recommends routine newborn screening at birth and then serum thyroid screening at 6 months, 1 year, and then annually in children with Down syndrome. (25)

CLINICAL FINDINGS AND DIAGNOSIS OF CH

The majority of cases of CH are asymptomatic at diagnosis. Symptoms may include increased sleep, constipation, and poor/slow feeding. On examination, neonates may have macroglossia, an umbilical hernia, dry skin, a coarse puffy face, and a widened anterior fontanelle with delayed reflexes and hypotonia on neurologic examination. In some cases of thyroid dysmorphogenesis, a goiter may be palpable. Prolonged neonatal jaundice, specifically conjugated hyperbilirubinemia, should be an indication to evaluate thyroid function as well as to assess for panhypopituitarism. If performed, radiography may reveal an absent femoral epiphysis because of delayed skeletal maturation in patients with severe hypothyroidism. (16)

Screening for early detection of primary hypothyroidism results in a diagnosis in 1 in 2,000 live births. (26) The pilot hypothyroidism screening programs were developed in Quebec, Canada, and Pittsburgh, PA, in 1974. In addition to clinical benefit, the cost of screening for CH is significantly lower than the cost of diagnosing CH at an older age. (14) The ideal time for newborn screening tests is 48 to 72 hours after birth to avoid the physiologic surge in TSH that occurs in the first hours after birth. To perform the newborn screen, capillary blood from a heel stick is placed on circles of specialized filter paper, dried, and then sent to a centralized laboratory. Figure 2 summarizes the algorithm for newborn thyroid screening. Initial screening varies by state, with 3 possible options: primary T₄ screening with reflex TSH if the T₄ value is below the cutoff, primary TSH screen, or combined TSH and T₄ screen. (15) TSH assays are becoming more accurate with small volumes of blood, so this is now the standard in most screening protocols. States with primary TSH screening may miss central hypothyroidism, while states with primary T₄ screening may miss cases of mild or subclinical hypothyroidism. (15) Samples taken within 48 hours of birth may lead to false-positive results, because the TSH value is physiologically elevated. Samples in sick newborns (with a delayed rise in TSH) or following blood transfusions may lead to false-negative results. Second screening at 2 to 4 weeks of age is becoming routine in certain programs. The addition of a second screen has diagnosed 1 in 30,000 neonates. A second screen should definitively be performed in preterm and low-birthweight infants, critically ill infants, same-sex twins, and infants with a first screen within the first 24 hours after birth. (27) However, screening should be performed before hospital discharge or a transfusion, even if it occurs before 48 hours after birth. (14) Kilberg et al reviewed the TSH cutoffs for 49 of the 50 newborn screen programs that process newborn screens received beyond the first 72 hours after birth. Of these programs, 24 do not adjust the TSH concentration cutoff according to an infant's age, and therefore cases of mild persistent CH may be missed. The use of age-adjusted TSH cutoffs in all screening programs is recommended. (28)

- TSH screening: If the TSH value is elevated (typically defined as >20–40 mU/L), confirmatory serum testing is required. A TSH value <20 mIU/L in the first 72 hours after birth is considered normal.
- Primary T₄ screening: If the T₄ value is less than the 10th percentile of the cutoff for all newborn screens that are done that day, TSH is performed on the same filter paper. If the TSH is not elevated, most screening programs require no further follow-up. States that require follow-up will either request a second

newborn screening test or recommend confirmatory serum testing. If the TSH is elevated, confirmatory serum testing is required.

If the newborn screen is positive, venipuncture blood is required to confirm the diagnosis of CH. Confirmatory serum tests should ideally be obtained in the first 2 weeks of age. Serum samples should be sent to measure the TSH level and either a total T₄ or FT₄ level. The total T₄ test is less expensive and can be reported within hours; however, FT₄ values are not affected by changes in TBG and represent the biologically relevant T₄. The results should be compared with age-normalized values for full-term and preterm infants. Prompt consultation with a pediatric endocrinologist is recommended if the results are abnormal for age. The TSH concentration is the most sensitive indicator of the HPT axis. Before age 2 weeks, venous TSH values greater than 20 mIU/L, and after 2 weeks, TSH values greater than 10 mIU/L suggest primary CH. Low serum T₄ or FT₄ with an elevated TSH confirms the diagnosis of primary hypothyroidism and treatment should be started immediately.

For subclinical hypothyroidism (also referred to as *hyperthyrotropinemia*) with a TSH value between 6 and 20 mIU/L with normal FT₄, it is reasonable to proactively monitor serum thyroid tests closely and defer starting LT₄ unless the TSH level continues to rise or the FT₄ level decreases to below normal.

As discussed earlier, there is no clinical evidence that thyroid hormone treatment is beneficial for preterm infants with physiologic hypothyroxinemia or hyperthyrotropinemia. Although some of these infants have a low T₄ level and a low or normal TSH level on the initial newborn screen, most will have normal results on the second or third newborn screen.

Additional investigations to identify the cause of the CH should not delay treatment decisions, though it may be useful for future decision making. Thyroid ultrasonography is usually the first test performed to determine the etiology of primary hypothyroidism. Color Doppler may be useful to identify an ectopic thyroid gland. An iodine uptake scan, with iodine 123 or sodium pertechnetate 99m, is the most accurate imaging tool to determine the size and location of the thyroid tissue. (29) It can be used to diagnose thyroid aplasia, hypoplasia, or an ectopic gland. Patients with blocking TRAbs, TSH receptor inactivating mutations, and iodine trapping defects will also not show any uptake but will have a normal or enlarged thyroid on ultrasonography. Alternatively, thyroglobulin levels may also be used to assess for the presence of a thyroid gland.

If the diagnosis of central hypothyroidism versus sick euthyroid is in question, testing for reverse T₃ or FT₄ levels with equilibrium dialysis measurements may be useful. (19) Patients with sick euthyroid syndrome typically have an elevated reverse T₃ level because of decreased metabolism of T₃. For patients found to have central hypothyroidism, it is crucial to screen for other pituitary deficiencies and to perform brain MRI.

If iodine excess or deficiency is a concern, a test of the infant's 24-hour urine iodine excretion may be useful, though challenging to obtain in neonates. The normal range is 50 to 100 mg/24 hours. (15)

In the setting of maternal Graves' disease, van der Kaay et al recommended using a neonatal Graves' risk assessment algorithm for neonates, based on the presence of maternal TRAbs. (23) If maternal serum TRAbs are positive or unknown, the TRAb level should be obtained from the cord blood or the neonate. Neonates with unknown or positive TRAb levels should be examined on the first day after birth, with follow-up examination and laboratory testing for TSH and FT₄ at 3 to 5 and 10 to 14 days of age. At that point, asymptomatic neonates with normal thyroid function can have routine follow-up at 1 month and 2 to 3 months of age. If the TRAb level is negative in the pregnant woman in the second or third trimester or from the cord/infant blood, the neonate is considered at low risk with no specific follow-up needed. If the thyroid function is abnormal or the newborn has clinical signs of hypo- or hyperthyroidism, prompt consultation with pediatric endocrinology is required for further management. (30)

MANAGEMENT OF CH

The timing and dosing of thyroid hormone replacement is crucial for neurodevelopment. LT₄ at 10 to 15 µg/kg per day is recommended and should be administered 30 minutes before feeding. The absorption is hindered by food and products with soy, iron, calcium, and aluminum. A crushed LT₄ tablet is typically mixed with 1 to 2 mL of breast milk, formula, or water and the suspension is placed in the cheek pad. Recently, a commercial levothyroxine sodium oral solution has been made available for the treatment of hypothyroidism and pituitary TSH suppression. It is the first liquid formulation of LT₄ approved by the Food and Drug Administration. However, the treatment of choice continues to be the tablet form of LT₄. If intravenous therapy is needed, the dose should be 50% to 80% of the oral dose. (31)

Treatment should be initiated within 2 weeks from birth. However, in patients with adrenal insufficiency in addition to central hypothyroidism or in those in whom adrenal insufficiency cannot be excluded, assessment of adrenal function, followed by adequate glucocorticoid therapy is needed for 48 to 72 hours before supplementing with LT₄, to prevent inducing an adrenal crisis.

The AAP recommends monitoring thyroid function 2 and 4 weeks after initiation of LT₄ treatment and every 1 to 2 months during the first 6 months of age. The goal is to normalize T₄ and TSH within 2 and 4 weeks, respectively. (14)(32) The target is T₄ and FT₄ concentrations in the upper half of the reference range for age, with normalization of TSH. (14)

Infants should be examined carefully for dysmorphic features, because congenital abnormalities are more common in patients with CH than in the general population. These abnormalities most commonly include heart defects, sensorineural hearing loss, or dysmorphic features. (15) Patients with syndromic features or a family history of hypothyroidism should be referred to genetics for further evaluation. For example, Pendred syndrome, from a defect in pendrin, which is a transmembrane chloride-iodide transporter, results in sensorineural deafness, hypothyroidism, and goiter. Bamforth-Lazarus syndrome is

caused by a mutation in thyroid transcription factor 2 and results in thyroid dysgenesis, choanal atresia, cleft palate, and spiked hair. (16)

Early detection and treatment of CH results in a near normal IQ, though mild brain impairment and discordance with family mental functioning may exist. The average IQ is approximately 6 points below expected, and there may be deficits in visuospatial, motor, language, memory, and attention tests. Mild sensorineural hearing loss also may be seen in up to 20% of cases. (33) Discontinuation of thyroid treatment before 3 years of age is not recommended. (26) For central hypothyroidism, cognitive deficits can be particularly severe if there is a delay in diagnosis. (19) Patients should be screened for problems with hearing and visual processing as well as for speech delay and referred to therapy if there are any concerns before 3 years of age. (31)

If there is no identified permanent cause of CH and no TSH increase after the newborn period with LT₄ treatment, the treatment should be discontinued after the child is 3 years old. The FT₄ and TSH should be measured 30 days later to determine if the child is euthyroid without the medication. If the TSH is elevated at 30 days, permanent hypothyroidism is diagnosed and LT₄ treatment should be resumed. If the results are inconclusive, repeat testing is needed. (14) Patients successfully weaned off LT₄ continue to require follow-up, while patients with permanent CH require LT₄ treatment for life.

SUMMARY

- Nationwide screening programs are the best method to diagnose CH (evidence level A). (14)(31)
- Diagnosis and treatment should be made in the first few weeks of age for optimal neurodevelopmental outcomes (evidence level A). (7)
- Imaging and further diagnostic evaluation should never delay treatment decisions (evidence level A). (14)(15)
- A clinical suspicion for hypothyroidism should be maintained in the right clinical setting, regardless of newborn screening results (evidence level A). (14)
- Repeat newborn screening should be performed in sick or premature infants at 3 to 4 weeks of age or before hospital discharge (evidence level A). (27)

ABBREVIATIONS

CH	congenital hypothyroidism
FT₄	free T ₄
HPT	hypothalamic-pituitary-thyroid
LT₄	levothyroxine
MRI	magnetic resonance imaging
T₃	triiodothyronine

T₄	thyroxine
TBG	thyroxine-binding globulin
TRAbs	thyrotropin receptor antibodies
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone (thyrotropin)

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Practice Gaps

1. Congenital hypothyroidism is one of the most common preventable causes of intellectual disability.
2. Newborn screening results in early treatment and diagnosis, potentially reducing the risk of irreversible intellectual disability and other comorbidities.
3. Clinicians should have a high clinical suspicion for congenital hypothyroidism, even with a normal result on newborn screening, because certain forms of central hypothyroidism or milder forms of primary congenital hypothyroidism may be missed.

Objectives

After completing this article, readers should be able to:

1. Interpret newborn screening results, recognize the importance of early screening, and describe the treatment of congenital hypothyroidism.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the physiological roles of the hormones and other proteins involved in the regulation of thyroid function.
- Know the relationship between fetal and maternal thyroid physiology.
- Know the embryology and normal physiological function of the thyroid gland.
- Know the proper use of laboratory tests (including screening tests) in the diagnosis of thyroid dysfunction.
- Know the etiology and clinical manifestations of congenital hypothyroidism.
- Know the laboratory features and approach to therapy of congenital hypothyroidism.
- Know how to evaluate and manage the causes of transient hypothyroidism in newborn infants.
- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis.

Figure 1.
Changes in serum thyroid-stimulating hormone (TSH) and thyroxine (T_4) concentrations in full-term and premature infants during the first 5 days of age.

Figure 2.

Newborn screening algorithm for congenital hypothyroidism. FT₄=free thyroxine; TSH=thyroid-stimulating hormone; T₄=thyroxine.