

Approach to the Diagnosis and Treatment of Neonatal Hypothyroidism

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Learning Objectives

Upon completion of this educational activity, participants should be able to:

- Select an optimal starting dose of levothyroxine in infants with congenital hypothyroidism, tailoring the dose to the severity of hypothyroidism
- Undertake tests to monitor thyroid hormone treatment at recommended intervals in the first three years of life in infants diagnosed with congenital hypothyroidism
- “Problem-solve” reasons for serum free T₄ and/or TSH levels outside the recommended target range (e.g, low levothyroxine dosing, problems with GI absorption, compliance issues) and fix the problem in infants diagnosed with congenital hypothyroidism.

Target Audience

This Journal-based CME activity should be of substantial interest to endocrinologists.

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Congenital hypothyroidism, occurring in 1:3000 newborns, is one of the most common preventable causes of mental retardation. Neurodevelopmental outcome is inversely related to the age of diagnosis and treatment. Infants detected through newborn screening programs and started on L-T₄ in the first few weeks of life have a normal or near-normal neurodevelopmental outcome. The recommended starting dose of L-T₄ (10–15 μg/kg · d) is higher on a weight basis than the dose for children and adults. Tailoring the starting L-T₄ dose to the severity of the hypothyroidism will normalize serum T₄ and TSH as rapidly as possible. It is important to obtain confirmatory serum thyroid function tests before treatment is started. Further diagnostic studies, such as radionuclide uptake and scan and ultrasonography, may be performed to determine the underlying cause of hypothyroidism. Because results from these tests generally do not alter the initial treatment decision, however, these diagnostic studies are rarely indicated. The developing brain has a critical dependence on thyroid hormone for the first 2–3 yr of life; thus, monitoring occurs at more frequent intervals than in older children and adults. Serum free T₄ and TSH should be checked at intervals frequent enough to ensure timely adjustment of L-T₄ dosing and to keep serum free T₄ and TSH levels in target ranges. Given the success of early detection and treatment of neonates with congenital hypothyroidism, a public health mandate should be to develop similar programs for the 75% of babies worldwide who are born in areas without newborn screening programs. (*J Clin Endocrinol Metab* 96: 2959–2967, 2011)

The Case

An 8-d-old neonate is referred for evaluation of abnormal newborn thyroid screening test results. This baby girl was the 3220-g product of a 42-wk, uncomplicated pregnancy, labor, and delivery. Mother is in good health; her only medication during pregnancy was a prenatal vitamin (which contained 150 μg of iodine). She has no history of a thyroid disorder; there is a family history of aunts with acquired hypothyroidism. Routine newborn screening tests on d 2 of life (on a heel prick blood specimen) returned with a T₄ of 4.5 μg/dl (<10th percentile) and a TSH of 632 mU/liter.

On evaluation at 8 d of age, the mother describes this as a “good baby,” already sleeping 6–8 h a night, in con-

Abbreviations: CH, Congenital hypothyroidism; DUOXA, dual oxidase; IQ, intelligence quotient; TBG, T₄ binding globulin; Tg, thyroglobulin; THOX, thyroid oxidase; TRB-Ab, TSH receptor-blocking antibody.

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trast to her first baby. Mother is breast-feeding, with no specific concerns, although she sometimes has to awaken the baby for a feeding. The baby initially had several soft bowel movements a day, now just one daily. On examination, weight is 3.4 kg (50th percentile), length is 49 cm (25th percentile), and head circumference is 35 cm (90th percentile). The sutures are easily palpable, and both the anterior and posterior fontanel are large for a newborn. Moderate jaundice is present on the chest and extremities. There are no dysmorphic features, and general examination is otherwise unremarkable. The referral requested that further diagnostic evaluation and management be undertaken, and, if congenital hypothyroidism (CH) is confirmed, that plans be developed for thyroid hormone dosing and monitoring of treatment.

Background

CH is one of the most common preventable causes of mental retardation. If the diagnosis of hypothyroidism is made and treatment started within a few weeks of birth, neurodevelopmental outcome generally is normal (1). The majority of newborns with CH do not have obvious manifestations of hypothyroidism, making clinical diagnosis difficult. This is because most infants have some residual thyroid function and because the clinical symptoms and signs of hypothyroidism are relatively nonspecific. Even infants with complete absence of thyroid hormone production appear to have some protection until birth as a result of transplacental passage of maternal thyroid hormone. Approximately one third of maternal T₄ crosses to the fetus at term (2). With a half-life of 6 d, this maternal T₄ will be metabolized and excreted by 3 to 4 wk of age. Over the first few weeks and months, more obvious symptoms and signs of hypothyroidism will develop, and worsening hypothyroxinemia will put the brain at risk for injury from hypothyroidism. Thus, there is some urgency to find and treat cases as soon after birth as possible. For all of the above reasons, the best way to detect infants with CH is by screening large populations of newborns. As technology allowed application of precise assays for measurement of T₄ and TSH in the small volume of blood obtained in newborn screening specimens, screening for CH was added to existing programs in the mid-1970s (3). Results from newborn screening programs in place for over three decades have provided a wealth of new information on CH.

Epidemiology

Before the onset of newborn screening, the incidence of CH based on clinical diagnosis was approximately 1:7000

TABLE 1. Etiology of CH

Primary CH
Thyroid dysgenesis
Aplasia
Hypoplasia
Ectopic gland
Thyroid dysmorphogenesis
Sodium-iodide symporter (trapping) defect
Thyroid peroxidase defect
Hydrogen peroxide generation or maturation defects
Tg defect
Deiodinase defect
Resistance to TSH binding or signaling
TSH receptor defect
G protein defect
Secondary (central) CH
Isolated TSH deficiency
Congenital hypopituitarism (multiple pituitary hormone deficiencies)
Peripheral CH
Thyroid hormone transport defect (monocarboxylase 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 TRB-Ab
Heterozygous THOX2 or DUOXA2 mutations
Congenital hepatic hemangiomas

(4). With the advent of newborn screening in the mid-1970s, the initial incidence was lower, 1:4000, with the obvious explanation that all cases now were detected by universal screening of a population of newborns. A more recent analysis reported that the incidence in the United States increased from 1:4094 in 1987 to 1:2372 in 2002 (5). Several factors appear to play a role in the increased incidence. With earlier discharge from the hospital, the screening specimen is obtained earlier, closer to the TSH surge after birth, resulting in more babies exceeding the TSH cutoff. Some programs also have lowered their TSH cutoff to prevent missing cases. Both of these changes will detect infants with milder CH not previously discovered (6). CH is more common in Asian, Native American, and Hispanic populations and less common in White and Black populations. Over the years described above, there has been a 37% increase in Asian births and a 53% increase in Hispanic births in the United States (7). CH is also higher in infants born to older mothers and in infants born preterm. The incidence of preterm births has increased 20% over the last 20 yr. Thus, multiple factors likely contribute to the reported increased incidence of CH.

Etiology (Table 1)

The most common cause of permanent primary CH is failure of the thyroid gland to develop properly (thyroid dysgenesis), a sporadic disorder that accounts for approx-

imately 85% of cases. An ectopic location of the thyroid gland accounts for approximately two thirds of thyroid dysgenesis, followed by aplasia or a hypoplastic (eutopic) gland. The exact underlying etiology for most cases of thyroid dysgenesis remains unknown. Although it would seem logical that mutations in transcription factor genes that regulate thyroid gland development [thyroid transcription factor 2 (TTF-2), NKX2.1 (also termed TTF-1) or PAX-8] would explain these defects, in fact, only 2% of cases with dysgenesis are found to have such genetic mutations (8). If present, these transcription factor mutations occur in other tissues and so are associated with syndromic CH; *e.g.* NKX2.1 mutations also occur in the lungs and brain, leading to CH, neonatal respiratory distress, and choreoathetosis. Resistance to TSH binding (TSH receptor defects) or signaling [G protein defects, *e.g.* pseudohypoparathyroidism (Albright's hereditary osteodystrophy)] results in eutopic thyroid hypoplasia.

The next most common cause of permanent primary CH is a defect in thyroid hormone production (thyroid dysmorphogenesis), which accounts for approximately 15% of cases. These hereditary defects are autosomal recessive and include mutations in the genes coding for the sodium-iodide symporter, thyroid peroxidase, hydrogen peroxide generation [thyroid oxidase and dual oxidase maturation factors (THOX and DUOXA)], thyroglobulin (Tg), and iodotyrosine deiodinase. Uncommon causes of CH include defects in thyroid hormone transport (mutations in the gene for monocarboxylase transporter 8), metabolism (selenocysteine insertion sequence-binding protein 2), or resistance to thyroid hormone action (mutations in the thyroid hormone receptor).

Transient CH is associated with excess maternal iodine ingestion (or deficiency), maternal ingestion of antithyroid drugs, maternal TSH receptor-blocking antibodies, heterozygous mutations of THOX2 or DUOXA2, and large congenital hepatic hemangiomas (increased type 3 deiodinase activity).

Although it is the intent of all newborn screening programs to detect infants with primary hypothyroidism, some programs detect infants with secondary (central) hypothyroidism (incidence 1:25,000–1:50,000) (9). These programs undertake a primary T₄ screening test and follow up infants with persistently low T₄ levels. The etiology of congenital central hypothyroidism includes cases with isolated TSH deficiency, most commonly due to mutations in the TSH β -subunit or in the TRH receptor gene. Most cases of congenital central hypothyroidism, however, are associated with other pituitary hormone deficiencies. These cases of congenital hypopituitarism may be due to mutations in transcription factor genes involved in pituitary gland development or function (HESX1, LHX4,

PIT1, and PROP1). Many of these cases are diagnosed when neonates present with clinical features, such as hypoglycemia (GH and/or ACTH/cortisol deficiency), micropenis and undescended testes (LH/FSH deficiencies), or with features of midline defects, such as decreased vision or nystagmus, as is seen in the syndrome of septooptic dysplasia.

Diagnostic Evaluation (Fig. 1)

In developed countries with newborn screening programs, essentially all infants with CH are diagnosed after detection by newborn screening tests. Worldwide, of an annual birth population of 127 million, however, it is estimated that only 25% of babies are born in countries with newborn screening programs in place (10). For the other 75%, diagnosis is made when development of suspicious clinical features leads to serum thyroid function testing.

Newborn thyroid screening test protocols

Newborn thyroid screening tests are carried out on heel-prick blood that is spotted on special filter paper cards. The specimen routinely is collected between 2 and 5 d of age, although in preterm or acutely ill term babies it may be collected as early as 1 h of age, upon admission to a neonatal intensive care unit. Some programs obtain a routine second specimen between 2 and 6 wk of age. The filter paper dried blood specimen is then mailed to a centralized laboratory.

Early in the history of screening newborns for CH, most programs undertook an initial T₄ test, with a “reflex” TSH test on babies with a T₄ level below a specified cutoff. With increasing accuracy of TSH assays on small blood volumes, many programs in the United States and worldwide have switched to an initial TSH test approach. The three newborn screening strategies are summarized as: 1) initial T₄ test—if result below specified cutoff, “reflex” TSH test; 2) initial TSH test; and 3) combined initial T₄ and TSH test.

Each newborn screening program sets cutoffs for test results. Generally, if the screening T₄ is below the 10th percentile and/or the TSH is greater than 30 mU/liter (>15 mU/liter whole blood), an infant is recalled for serum testing. In cases with “intermediate results,” *e.g.* low T₄ but TSH below cutoff, a program may recommend that a repeat heel prick screening specimen be collected and sent for analysis.

Although there are pros and cons to a primary T₄ *vs.* primary TSH screening test strategy, the main advantage of the primary T₄ (and combined T₄ and TSH) test is the ability to detect neonates with congenital secondary (cen-

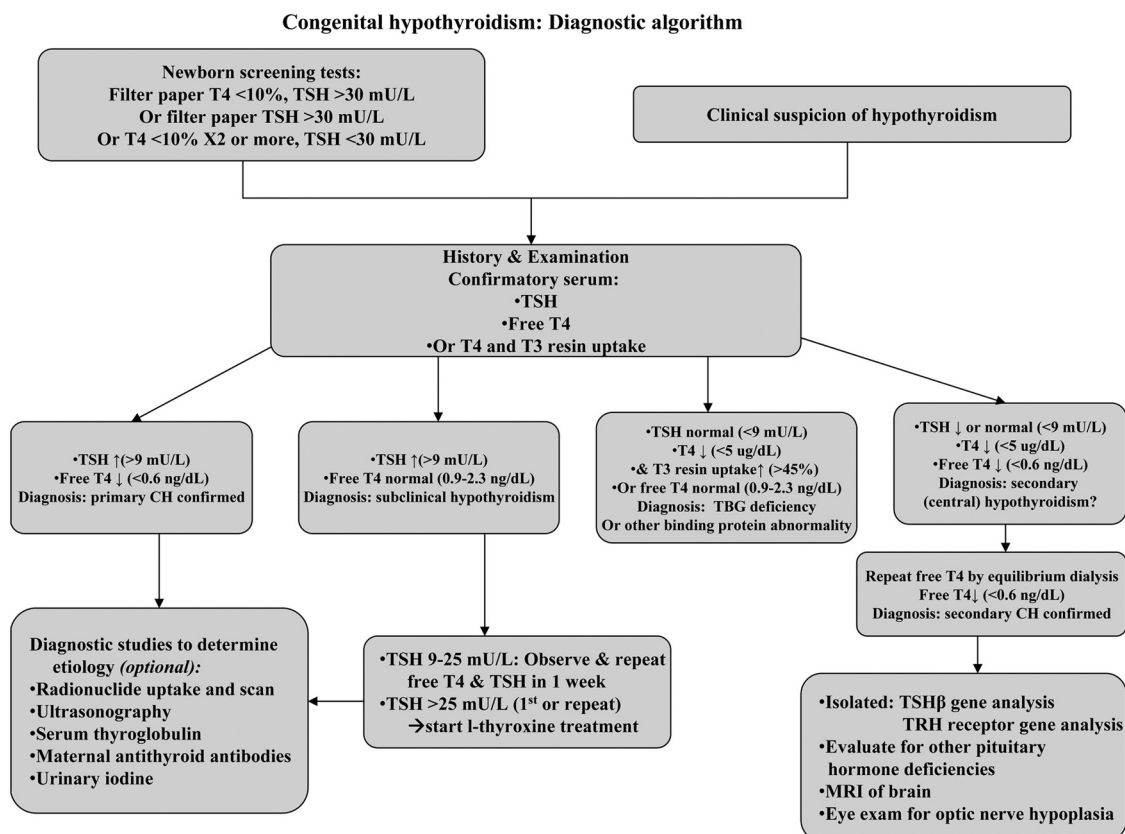


FIG. 1. Diagnostic algorithm for congenital hypothyroidism. Note that each screening program sets its own T_4 and TSH cutoffs. The results for serum TSH, free T_4 , T_4 , and T_3 resin uptake are typical for neonates around 2 wk of age. It is important for clinicians to compare serum results to age-normal reference ranges for their specific laboratory.

tral) hypothyroidism. Such patients have the same degree of hypothyroidism as many infants with primary hypothyroidism and so are likely at risk for the same degree of developmental impairment. This is the reason we in the Northwest Regional screening program have chosen not to switch to a primary TSH test approach. (For more details on the advantages and disadvantages of each screening test strategy, see Ref. 11.)

Confirmatory serum thyroid testing

Neonates with abnormal thyroid screening tests should be recalled immediately for examination, and a venipuncture blood sample should be obtained for confirmatory serum testing. Diagnosis and treatment should not be based on screening test results alone. Confirmatory serum should be tested for TSH and free T_4 , or total T_4 combined with some measure of binding proteins such as a T_3 resin uptake. Serum TSH and T_4 undergo dynamic changes in the first weeks of life; it is important to compare serum results to age-normal reference ranges (12). Most confirmatory serum testing is obtained around 1 to 2 wk of age, when the upper TSH range has fallen to approximately 10 mU/liter. An infant with an elevated serum TSH level and a low free T_4 or total T_4 is confirmed to have primary hypothyroidism. The finding of an elevated serum TSH

but normal free T_4 or total T_4 is consistent with subclinical hypothyroidism. Clinical judgment is required to determine whether to start thyroid hormone treatment or monitor thyroid function tests in cases of mild subclinical hypothyroidism (Fig. 1). For example, if the serum TSH is mildly elevated (9–25 mU/liter) and appears to be decreasing compared with the screening TSH level, it may be prudent to hold off treatment and recheck a serum TSH and free T_4 in 1 wk. If the serum TSH has not normalized by 3–4 wk of age, we recommend treating. If the initial TSH is greater than 25 mU/liter or fails to trend toward normal, we also recommend starting thyroid hormone treatment.

In programs that employ a primary T_4 screening test, preterm and/or low birth weight babies typically have a low T_4 but normal range TSH level. The T_4 value generally rises into the normal range by 6 wk of age. Programs that follow up with cases of persistently low T_4 levels may detect patients with central hypothyroidism or binding protein abnormalities. Infants with a low serum free T_4 level and low or normal-range TSH on confirmatory testing may have secondary (central) hypothyroidism. Clinicians should bear in mind that the most commonly employed free T_4 assays (analog method) may yield artificially low results in certain situations, such as preterm

infants with low serum binding protein concentrations or acutely ill infants with “nonthyroidal illness syndrome.” Thus, we recommend repeating a serum free T_4 with measurement by the equilibrium dialysis method to confirm a diagnosis of central hypothyroidism. Infants with a low serum total T_4 and normal-range TSH may have central hypothyroidism, but more commonly they have T_4 binding globulin (TBG) deficiency. An elevated serum T_3 resin uptake points to low binding protein levels. Measurement of serum TBG will confirm the diagnosis. Serum free T_4 levels are normal in infants with TBG deficiency, and no treatment is indicated.

Diagnostic studies to determine underlying etiology

Once an infant is confirmed to have primary CH, additional diagnostic studies may be undertaken to determine a specific etiology. Results from these diagnostic tests generally do not alter the initial treatment decision, and so, many screening programs consider them optional. There are uncommon cases where additional diagnostic studies help determine whether or not to start thyroid hormone treatment, but for the majority of cases, these additional studies are rarely indicated. Starting thyroid hormone treatment should never be delayed by more than a few days to perform these additional studies.

Thyroid radionuclide uptake and scan

Radionuclide uptake and scanning are the most accurate imaging tests to define the size and location of any thyroid tissue. Iodine-123 (I-123) or sodium pertechnetate 99m (Tc 99m) should be used in neonates; I-131 delivers too high a dose of radioactivity to the thyroid and total body. Radionuclide uptake and scan may identify thyroid aplasia, hypoplasia (decreased uptake, small gland in a eutopic location), or an ectopic gland (small gland located somewhere between the foramen cecum and eutopic location over the thyroid cartilage). Absent uptake, typically diagnostic of thyroid aplasia, can also be seen with TSH β gene mutations, TSH receptor-inactivating mutations, iodide-trapping defects, and maternal TSH receptor-blocking antibodies (TRB-Ab). Thus, infants with absent uptake should be evaluated further by thyroid ultrasonography (see below).

A large gland with increased uptake is compatible with one of the inborn errors of thyroid hormone production beyond trapping of iodide (dyshormonogenesis). A perchlorate discharge test may be helpful in identification of defective oxidation and organification. If an inborn error of thyroid hormone production is suspected, genetic tests to identify the specific defect may be undertaken.

Thyroid ultrasonography

Absent radionuclide uptake should be followed by an ultrasound examination to confirm thyroid aplasia. Absent uptake but with a small-to-normal sized gland in a eutopic location determined by ultrasonography may be explained by TSH β gene mutations, TSH receptor-inactivating mutations, iodide-trapping defects, and transplacental passage of maternal TRB-Ab. Specific genetic testing or measurement of maternal TRB-Ab will help to separate out these possibilities. Ultrasonography is not as accurate as radionuclide scanning in detection of an ectopic thyroid, although Doppler ultrasonography is reported to identify up to 90% of ectopic glands (13). As with radionuclide scanning, a large gland is suggestive of one of the dyshormonogeneses.

Serum Tg determination

Serum Tg levels may be helpful in further evaluation of infants with absent radionuclide uptake or increased uptake with a large gland. In infants with absent uptake, low serum Tg levels are consistent with thyroid aplasia, whereas increased Tg levels are compatible with TSH receptor-inactivating mutations, iodide-trapping defects, or maternal TRB-Ab. In infants with a large gland, an elevated serum Tg level is suggestive of a Tg gene mutation.

Serum TRB-Ab determination

The combination of absent radionuclide uptake and a small or normal eutopic gland determined by ultrasonography in an infant born to a mother with autoimmune thyroid disease is strongly suggestive of CH resulting from transplacental passage of maternal TRB-Ab. This disorder can be confirmed by measurement of serum TRB-Ab in mother and/or infant. TRB-Ab can be evaluated by a TBII (thyrotropin-binding inhibitor immunoglobulin) test.

Urinary iodine determination

In an infant with CH born in an area of endemic iodine deficiency, measurement of urinary iodine will confirm low iodine levels. Urinary iodine approximates iodine intake; the normal range in neonates is approximately 50 to 100 $\mu\text{g}/24\text{ h}$. If there is a history of excess iodine ingestion in the mother or iodine exposure in the neonate, for example from iodine-containing skin antiseptics, a urinary iodine determination will confirm this diagnosis.

Studies to detect associated congenital anomalies

Although major congenital anomalies occur in 3% of the normal population, they are reported to occur in up to 10% of newborns with CH (14). The most common associated defect is a congenital heart anomaly. There is no consensus on undertaking screening tests for associated

congenital anomalies. A careful physical examination is important, and any cardiac findings should be evaluated further by echocardiography. A hearing problem is reported in up to 20% of infants with CH; all infants with CH should undergo screening hearing tests.

Treatment

The timing, starting L-T₄ dose, and monitoring of treatment are crucial in ensuring the best neurodevelopmental outcome in patients with CH. There is an inverse relationship between the age of diagnosis/treatment and intelligence quotient (IQ). In one study from the prescreening era, infants diagnosed by 3 months of age had a mean IQ of 89, and those diagnosed between 3 and 6 months had a mean IQ of 71, whereas if diagnosis was delayed to more than 6 months of age, the mean IQ fell to 34 (15). Infants detected by newborn screening programs and started on treatment in the first few weeks of life generally have an IQ in the normal range, although some studies show subtle deficits in neurocognition (1). Several studies have correlated these subtle deficits with later onset of treatment, lower starting thyroid hormone dosing, and severity of the hypothyroidism, which itself correlates with the underlying etiology.

Thyroid hormone formulation

L-T₄ is the treatment of choice. Although T₃ is the biologically active form of thyroid hormone, studies show that most T₃ in the brain is formed from local deiodination of T₄. Studies of L-T₄ treatment alone report normal serum T₃ levels in infants with CH (16). Thus, T₃ replacement is not necessary for normal neurodevelopment.

Currently, only L-T₄ tablets are approved for treatment in the United States. Thyroid hormone suspensions compounded by individual pharmacies may vary in potency and result in unreliable dosing. In Europe, however, a liquid form of L-T₄ (manufactured by Henning Berlin) resulted in normalization of thyroid function similar to tablets (17).

Dosage

The initial L-T₄ dose for infants with CH recommended by the American Academy of Pediatrics and the European Society for Pediatric Endocrinology guidelines is 10–15 $\mu\text{g}/\text{kg} \cdot \text{d}$ (Table 2) (18, 19). Studies show that starting L-T₄ doses in this range will normalize serum free T₄ or T₄ in 3 d and TSH in 2–4 wk (20). Rapid normalization of thyroid function has been demonstrated to be important in achieving optimal neurodevelopmental outcome. For example, in one study a delay in normalizing serum T₄ and

TABLE 2. Starting L-T₄ dose, monitoring, and target ranges for serum free T₄ and TSH on treatment

Starting L-T ₄ dose: 10–15 $\mu\text{g}/\text{kg} \cdot \text{d}$
Monitoring serum free T ₄ (or total T ₄) and TSH:
At 2 and 4 wk after initiation of L-T ₄ treatment
Every 1 to 2 months during the first 6 months of life
Every 2 to 3 months between 6 months and 3 yr of age
Every 6 to 12 months until growth is complete
4 wk after a change in L-T ₄ dosage
Target ranges for serum free T ₄ , total T ₄ , and TSH on treatment:
Free T ₄ : upper half of reference range for age
Example: reference range, 0.8–2.3 ng/dl, aim for 1.4–2.3 ng/dl
Total T ₄ : 10–16 $\mu\text{g}/\text{dl}$ in the 1st 2 yr of life; thereafter, upper half of reference range for age
TSH: <5 mU/liter, optimally 0.5–2.0 mU/liter

TSH by more than 2 wk after starting treatment resulted in a 10 point lower IQ (21).

It also appears to make sense to tailor the initial L-T₄ dose within the 10–15 $\mu\text{g}/\text{kg} \cdot \text{d}$ range to the severity of hypothyroidism. In another study, infants with athyreosis were started on 15 $\mu\text{g}/\text{kg} \cdot \text{d}$, infants with an ectopic gland were started on 12 $\mu\text{g}/\text{kg} \cdot \text{d}$, whereas infants with dyshormonogenesis were started on 10 $\mu\text{g}/\text{kg} \cdot \text{d}$ (22). Seventy-eight percent of infants normalized free T₄ within 7 d and all by 14 d of treatment. Although the variable-dosing paradigm in this study was based on etiology, it makes as much (if not more) sense to base it on pretreatment serum free T₄ or T₄ levels. In the study referenced above, the mean free T₄ level in the group with athyreosis was 0.12 ng/dl; in the ectopic group, 0.44 ng/dl; and in the dyshormonogenesis group, 0.45 ng/dl (22).

Administration

The daily L-T₄ tablet should be crushed and mixed with water, expressed breast milk, or formula. The resulting suspension can be drawn up in a syringe and squirted into the cheek pad or put in an open nipple for the infant to suck. L-T₄ should not be mixed with substances that interfere with gastrointestinal absorption, such as soy protein formula, concentrated iron, or calcium. Although it is recommended to administer L-T₄ on an empty stomach and avoid food for 30–60 min, this is not practical in an infant. As long as the method of administration is consistent day to day, dosing can be adjusted based on serum thyroid test results to achieve the treatment goals (23).

Target serum free T₄/total T₄ and TSH goals on treatment

Guidelines for target serum free T₄ or total T₄ and TSH levels on treatment recommended by the American Academy of Pediatrics (18) and the European Society for Pediatric Endocrinology (19) are presented in Table 2. Main-

tenance of serum thyroid function tests in these target ranges is important in ensuring optimal neurodevelopmental outcome. For example, the New England Collaborative reported that persistent serum T_4 below 10 $\mu\text{g}/\text{dl}$ in the first year of life was associated with an 18-point lower IQ compared with patients with T_4 above 10 $\mu\text{g}/\text{dl}$ (24). Care also must be taken to avoid prolonged overtreatment. Prolonged overtreatment may lead to craniosynostosis and temperament problems (25).

Monitoring

The developing brain has a critical dependence on thyroid hormone for the first 2–3 yr of life. The treating physician must monitor thyroid function tests at intervals frequent enough to ensure timely adjustment of thyroid hormone dosing so as to keep the serum free T_4 or total T_4 and TSH levels in the target ranges. The American Academy of Pediatrics (18) and the European Society for Pediatric Endocrinology (19) guidelines for monitoring serum free T_4 or total T_4 and TSH are shown in Table 2. Laboratory testing may be necessary at more frequent intervals when compliance is questioned, abnormal values are obtained, or the source of medication has been changed.

Clinical evaluation can be carried out at less frequent intervals than laboratory evaluation. The overall goal of treatment is to ensure that infants with CH have growth and neurodevelopmental outcomes as close as possible to their genetic potential.

Controversies and Areas of Uncertainty

Second routine or discretionary screening test

Those programs that collect a routine second specimen report that approximately 10% of CH cases “pass” the first test and are detected by an abnormality on the second screening test (26). Those programs that undertake a single test have not heard of “missed” cases, so they are skeptical that the CH cases detected on the second test are “real.” However, essentially every program that has gone on to undertake a second routine test detects an additional 10–15% of cases (27). One category of cases detected on the second specimen is infants with delayed TSH elevation. These cases have a low T_4 but a normal TSH level on the first specimen, whereas on the second specimen the T_4 remains low but the TSH level is now elevated. Infants born preterm or acutely ill term infants are those most at risk for delayed TSH elevation. The incidence of delayed TSH elevation is reported to be approximately 1:18,000 (28). With recognition that infants with delayed TSH elevation will be missed on the first specimen, many pro-

grams have elected to add a “discretionary” second specimen in preterm or acutely ill neonates. The explanation for the delayed TSH elevation is uncertain; a recent study appears to show that the majority of cases have transient hypothyroidism, with thyroid function reverting to normal without treatment in most cases (29).

In this context, we need to remember that the purpose of detecting CH is to prevent developmental disability. A recent review of outcomes in the prescreening era concludes that only children with moderate or severe CH likely benefit from early detection and treatment and argues that detection of milder forms of CH is not cost-effective (30). Thus, whether newborn screening programs need to collect a routine or discretionary second specimen remains controversial.

Increasing incidence

As described under *Epidemiology* above, the incidence of CH appears to have nearly doubled in the United States from 1987 to 2002 (5). The factors cited, including a lowering of screening test cutoffs, a change in birth population demographics, and an increase in preterm births, appear to only partially explain the increased incidence (7). This then leads to questions about whether something else has changed, causing an increase in CH cases. There is uncertainty about whether this increased incidence is real, but potential explanations including a decrease in maternal iodine intake or an environmental agent toxic to the thyroid gland are being investigated (31, 32).

Etiology of thyroid dysgenesis

As noted above under *Etiology*, investigations of mutations in genes coding for transcription factors regulating thyroid gland development have not disclosed a specific etiology in the majority of cases of thyroid dysgenesis. Some investigators have suggested that a combination of hereditary and epigenetic factors may underlie this disorder (33). As noted above, many clinicians/programs do not undertake diagnostic studies to determine an underlying cause of CH because the initial treatment decision is based primarily on thyroid function test results. However, I think it is important for a cohort of infants to continue to undergo these additional diagnostic studies to identify cases of thyroid dysgenesis for further investigation of a specific etiology. This is most easily done in geographic programs where all infants are referred to a central specialty unit.

Monitoring

As noted above, monitoring of thyroid function tests must be frequent enough to allow timely adjustments in L- T_4 dosing. A recent study takes issue with the recom-

recommendations of the American Academy of Pediatrics to undertake laboratory tests “every 3 to 4 months between 6 months and 3 yr of age” (34). This study reports that testing every 3 to 4 months risks some infants being undertreated for a few months. I agree, and so I changed this recommendation to testing “every 2 to 3 months between 6 months and 3 yr of age” (Table 2).

Monitoring also may address the issue of whether a case is permanent or transient CH. Cases are determined to be permanent if a specific cause is identified, *e.g.* thyroid dysgenesis or dyshormonogenesis, or if there is a rise in serum TSH level to greater than 10 mU/liter after the first year of life with insufficient L-T₄ treatment. If this question has not been answered by age 3 yr, guidelines recommend discontinuation of L-T₄ for 30 d and reassessment of thyroid function by measurement of serum free T₄ and TSH levels (18, 19). Systematic studies are needed in infants detected by abnormalities on a second screening test, in particular those with delayed TSH elevation, to confirm whether or not these infants have transient or permanent hypothyroidism. These results will help determine whether programs should modify their screening test approach to detect and treat such cases.

Returning to the Case

As illustrated by our patient, most newborn infants with CH do not have clinical manifestations leading to a suspicion of hypothyroidism until notification from the newborn screening program. Once the diagnosis is suspected, clinical features consistent with CH may be recognized. About one third of babies have gestation of at least 42 wk. Infants with CH have normal birth weight and length, but head circumference is relatively larger, owing to cerebral myxedema. Common findings on physical examination include large fontanelles (thyroid hormone regulates skeletal maturation) and jaundice (thyroid hormone is necessary for maturation of liver enzymes, including glucuronyl transferase). Unfortunately, a “good baby” who sleeps through the night in the first weeks of life is too good to be true, and needing to be awakened for a feeding is not normal.

The next step was to obtain serum thyroid function tests to confirm the diagnosis. This infant was started on 50 µg/d of L-T₄, pending serum results. Based on the screening tests, she was judged to have moderate-to-severe hypothyroidism, and so the initial dose of L-T₄ was selected in the upper end of the recommended range. At a current weight of 3.4 kg, this was equivalent to 14.7 µg/kg · d. Mother was instructed to crush up the daily pill and mix with expressed breast milk. She was given disposable

plastic syringes to draw up this suspension and squirt it into the cheek pad before a feeding. Serum test results on d 8 of life confirmed the diagnosis of CH: free T₄, 0.42 ng/dl (0.9–2.3 ng/dl); and TSH, 548 mU/liter. Her treating physician chose not to undertake any further diagnostic studies.

At 2 wk into treatment, serum free T₄ was 2.2 ng/dl and TSH was 18 mU/liter. At 4 wk, serum free T₄ was 2.8 ng/dl and TSH was 0.30 mU/liter (0.34–5.60). At that point, the dose of L-T₄ was reduced to 37.5 µg/d. One month later, serum free T₄ was 2.0 ng/dl, and TSH was 1.9 mU/liter. Serum free T₄ and TSH will be measured every 1 to 2 months up to 6 months of age and then every 2 to 3 months until age 3 yr of age. Growth and development have been normal.

Conclusion

The neurodevelopmental outcome in children with CH detected by newborn screening and started on thyroid hormone treatment early is normal or near-normal. Newborn screening for CH has been a great success story and hopefully will continue to expand worldwide. As has been the experience with all new disorders added to existing programs, when a large birth population undergoes comprehensive screening, new and previously undescribed forms of thyroid dysfunction are discovered. CH encompasses a group of disorders running the spectrum from severe, permanent hypothyroidism to mild, transient hypothyroidism. The specific etiology for the most common cause of CH, thyroid dysgenesis, however, remains largely unknown and awaits a scientific breakthrough. The apparent doubling of the incidence of CH is partially explained, but it needs further investigation and confirmation. The issues of possible emerging maternal iodine deficiency in the United States or environmental agents toxic to the thyroid gland need to be resolved. The significance of thyroid dysfunction characterized by delayed elevation of serum TSH in preterm infants and acutely ill term infants needs further evaluation. Is this a benign, transient form of hypothyroidism, or should these infants be treated to protect their developing brains until thyroid function recovers? It is important not to lose sight of the factors that we know determine neurodevelopmental outcome. Although we cannot change any effect of prenatal thyroid deficiency, we can start treatment in a timely fashion, tailoring the starting L-T₄ dose to the severity of hypothyroidism. And, we can ensure appropriate monitoring of thyroid function and dose adjustment during the critical first 3 yr of treatment.

Acknowledgments

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