Congenital Hypothyroidism

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INTRODUCTION

Thyroid hormones are essential for normal development and growth of many target tissues, including the brain and the skeleton. Thyroid hormone (TH) action on critical genes for neurodevelopment is limited to a specific time window, and even a short period of deficiency of TH can cause irreversible brain damage**.** During the first trimester of pregnancy fetal brain development is totally dependent on maternal thyroid function. Congenital hypothyroidism (CH) is one of the most preventable causes of mental retardation, but early diagnosis is needed in order to prevent irreversible damage. Today more than 70% of the babies worldwide are born in areas without an organized screening program. Screening for CH has enabled the virtual eradication of the devastating effects of mental retardation due to sporadic CH in most developed countries of the world. The survival of increasingly small and premature fetuses has resulted in a growing number of neonates with abnormalities in thyroid function and a continuing controversy as to which of these infants require therapy.

Non endemic CH is one of the commonest treatable causes of mental retardation. The importance of early treatment in diminishing the neuro-psychological abnormalities of CH was demonstrated convincingly in the 1970's. The development of a sensitive and specific radioimmunoassay for the measurement of T4 in dried whole blood and later tests for T4 and TSH using 1/8″ discs provided the technical means to screen all newborns for CH prior to the development of clinical manifestations. Thus, CH includes all the characteristics of a disease for which screening is justified: 1) it is common (4-5 times more common than phenylketonuria for which screening programs were initially developed); 2) to prevent mental retardation, the diagnosis must be made early, preferably within the first few days of life; 3) at that age, clinical recognition is difficult if not impossible; 4) sensitive, specific screening tests are available; 5) simple, cheap effective treatment is available; and 6) the cost-benefit ratio is highly favorable. Newborn screening programs have been introduced throughout the industrialized nations and are under development in many other parts of the world. Although there continues to be some disagreement as to whether minor neuro-intellectual sequelae remain in the most severely affected infants, accumulating evidence suggests that a normal outcome is possible even in the latter group of babies as long as treatment is started sufficiently early and is adequate.

National screening programs are well organized in many developed countries. However, it must be emphasized that approximately 71% of babies worldwide are not born in an area with an established national screening program for CH. The economic burden of disability owing to CH is still a significant

public health challenge.

CLINICAL RECOGNITION

Clinical findings of CH are usually difficult to appreciate in the newborn period except in the unusual situation of combined maternal-fetal hypothyroidism. Many of the classic features (large tongue, hoarse cry, facial puffiness, umbilical hernia, hypotonia, mottling, cold hands and feet and lethargy), when present, are subtle and develop only with the passage of time. In addition to the aforementioned findings, nonspecific signs that suggest the diagnosis of neonatal hypothyroidism include: prolonged, unconjugated hyperbilirubinemia, gestation longer than 42 weeks, feeding difficulties, delayed passage of stools, hypothermia, or respiratory distress in an infant weighing over 2.5 kg. A large anterior fontanelle and/or a posterior fontanelle > 0.5 cm is frequently present in affected infants but may not be appreciated. In general, the extent of the clinical findings depends on the cause, severity, and duration of hypothyroidism. Babies in whom severe feto-maternal hypothyroidism was present in utero tend to be the most symptomatic at birth. Similarly, babies with athyreosis or a complete block in thyroid hormonogenesis tend to have more signs and symptoms at birth than infants with an ectopic thyroid, the most common cause of CH. Unlike acquired hypothyroidism, babies with CH are of normal size. However, if diagnosis is delayed, subsequent linear growth is impaired. The finding of palpable thyroid tissue suggests that the hypothyroidism is due to an abnormality in thyroid hormonogenesis or in thyroid hormone action.

Bone maturation reflects the duration and the severity of hypothyroidism. Signs of delayed epiphyseal maturation on knee x-rays, persistence of the posterior fontanelle, a large anterior fontanelle, and a wide sagittal suture all reflect delayed bone maturation. The absence of one or both knee epiphyses has been shown to be related to T4 concentration at diagnosis and to IQ outcome, and is thus a reliable index of intrauterine hypothyroidism.

PATHOPHYSIOLOGY

For a detailed discussion of the cause of CH and hypothyroidism in infants see the chapter in Endotext entitled Disorders of the Thyroid Gland in Infancy, Childhood and Adolescence by Segni in the Thyroid section.

Permanent Primary Congenital Hypothyroidism

Permanent primary CH can be the consequence of a disorder in thyroid development and/or migration (thyroid dysgenesis), or due to defects at every step-in thyroid hormone synthesis (thyroid dyshormonogenesis). Although CH is in the great majority of cases a sporadic disease, the recent guidelines for CH recommend genetic counseling in targeted cases. Positive family history for CH, association with cardiac or kidney malformation, midline malformations, deafness, neurological sigs (i.e., choreoathetosis, hypotonia), any sign of Albright hereditary osteodystrophy, lung disorders, suggest genetic counseling, in order to assess the risk of recurrence and to provide further information about a possible genetic etiology of CH. Genetic causes of CH are described in table 1.

TABLE 1. GENETIC CAUSES OF CONGENITAL HYPOTHYROIDISM		
	Gene locus	**Inheritance**
PRIMARY HYPOTHYROIDISM		
Monogenic forms of thyroid dysgenesis		

Thyroid stimulating hormone receptor (TSHR)		AR
NK2 1 (NK2-1, TTF1) brain-lung thyroid syndrome	14q13	AD
Paired box gene 8 (PAX8)	2q11.2	AD
Forkhead boxE1 (FOXE1, TTF2) (Bambforth-Lazarus syndrome)	9q22	AR
NK2 homeobox 5 (NKX2-5)		
New candidate genes		
Nertrin 1 (NTN-1)		
JAG1	20p.12.2	
Glis3	9p24.2	AR
Inborn errors of thyroid hormonogenesis		
Sodium/Iodide symporter (SLC5A5, NIS)	19p13.2	AR
Thyroid peroxidase (TPO)	2p25	AR
Pendred syndrome (SLC26A4, PDS)	7q31	AR
Thyroglobulin (TG)	8q24	AR
Iodothyrosine deiodinase (IYD, DEHAL1)	6q24-25	AR
Dual oxidase 2 (DUOX2)	15q15.3	AR/AD
Dual oxidase maturation factor 2 (DUOXA2)		AR/AD
CENTRAL HYPOTHYROIDISM		
Isolated TSH deficiency		
TRHR	14q31	AR
TSHB	1p13	AR
Isolated TSH deficiency or combined pituitary hormone deficiency		
Immunoglobulin superfamily member1 (IGSF1) gene defects	Xq26.1	X-Linked
Combined pituitary hormone deficiency		
POU1F1	3p11	AR, AD
PROP1	5q	AR
HESX1	3p21.2-21.2	AR/AD
LHX3	9q.34	AR
LHX4	1q25	AD
SOX3		X-linked
OTX2		AD

THYROID DYSGENESIS

The majority (85 to 90%) of cases of permanent CH in North America, Western Europe, and Japan are due to an abnormality of thyroid gland development (thyroid dysgenesis). Thyroid dysgenesis may result in the complete absence of thyroid tissue (agenesis, 20-30%) owing to a defect in survival of the thyroid follicular cells precursors) or it may be partial (hypoplasia); the latter often is accompanied by a failure to descend into the neck (ectopy) mostly located in a sublingual position as a result of a premature arrest of its migratory process. Lowering of cut off TSH values for newborn screening increases the percentage of CH with thyroid in situ. Females are affected twice as often as males. In the United States,

thyroid dysgenesis, is less frequent among African Americans and more common among Hispanics and Asians. Babies with CH have an increased incidence of cardiac anomalies, particularly atrial and ventricular septal defects. An increased prevalence of renal and urinary tract anomalies has also been reported. Most cases of thyroid dysgenesis are sporadic. Familial cases represent approximately 2% of cases.

Genetic causes of congenital hypothyroidism are described in table 1. Thyroid transcription factors (TTF) such as NKX2-1 (or formerly TTF1/TITF1), FOXE1 (Forkhread Box E1, formerly TTF2/TITF2), PAX8 (Paired box gene 8), and NKX2-5, are expressed during early phases of thyroid organogenesis (budding and migration), and thyroid stimulating hormone receptor gene (TSHR) is expressed during the later phases of thyroid development. All these genes are involved in normal thyroid development and in thyroid dysgenesis, however, abnormalities in these genes have been found in only a small proportion of affected patients, usually in association with other developmental abnormalities. Alternately, epigenetic modifications, early somatic mutations, or stochastic developmental events may play a role. Five monogenic forms due to mutations in TSHR, NXK2-1, PAX8, FOXE-1. NXK2-5 have been reported. Monogenic forms represent less than 10% in thyroid dysgenesis. Inactivating TSHR mutations are the most frequent cause of monogenic thyroid dysgenesis and non-syndromic CH, with prevalence in CH cohorts around 4 %.

INBORN ERRORS OF THYROID HORMONOGENESIS

Inborn errors of thyroid hormonogenesis (thyroid dyshormonogenesis) are responsible for most of the remaining cases (15%) of neonatal thyroidal hypothyroidism. Unlike thyroid dysgenesis, most are sporadic condition. These inborn errors of thyroid hormonogenesis are commonly associated with an autosomal recessive form of inheritance, consistent with a single gene abnormality. DUOX2 mutations can be transmitted in autosomal dominant way. Thyroid dyshormonogenesis is caused by genetic defects in proteins involved in all steps of thyroid hormone synthesis and often associated with goiter formation. Goiter can be present in utero or at birth. .A number of different defects have been characterized based on radioiodine uptake and perchlorate test and include: 1) Iodide transport defect that shows failure to concentrate iodide, with low or absent radioiodine uptake; 2) Iodide organification defects due to thyroid peroxidase mutations (TPO), Dual Oxidase 2 (DUOX2), Dual Oxidase Maturation Factor 2 mutations (DUOX2A), SLC26A4, and pendrin defects that have normal radioiodine uptake and altered perchlorate discharge test; and *3*) Forms with normal radioiodine uptake and a normal perchlorate test due to thyroglobulin TG mutations, iodide recycling defects, and iodothyrosine deiodinase mutations.

PENDRED SYNDROME

Pendred syndrome is defined by the association of familial profound deafness with multinodular goiter. It is caused by biallelic mutation in the pendrin gene. Pendred syndrome is the only form of thyroid dyshormonogenesis associated with a malformation. The inner ear presents a characteristic malformation of the cochlea. Congenital hypothyroidism is present in only 30% of cases, goiter occurs often in childhood. Perchlorate test shows a partial organification defect. Pendred syndrome is the most frequent etiology of familial deafness.

Central Congenital Hypothyroidism (CCH)

CCH is caused by an insufficient thyroid hormone biosynthesis due to a defective stimulation by TSH, in the presence of an otherwise normal thyroid. This

condition includes all causes of CH due to a pituitary or hypothalamic pathology (secondary or tertiary hypothyroidism). CCH was previously considered a very rare disease with a prevalence initially estimated to be 1:100,000 in newborns. In more recent data, CCH had an incidence that could reach 1:16,000, as shown from results from screening for CH in the Netherlands.

CCH is sometime not identified at birth, because the limiting step is "how low is a low T4", low enough to be considered an effective cutoff value and allow the determination of TSH and TBG. Many cases are diagnosed in infancy or childhood, if not later in adulthood. The majority of screening programs are based on TSH determination and a high index of suspicion is needed to identify CCH in the preclinical phase. Delayed diagnosis may result in neurodevelopment delay. More than 50% of children with CCH have moderate or severe hypothyroidism, so, if not treated, the risk of neurodevelopmental delay should not be underestimated.

In the majority of cases identified early, TSH deficiency is a part of combined pituitary hormone deficiency. A timely correction of ACTH and cortisol deficiency, and/or GH deficiency may avoid life threatening emergencies. CCH can be transient (mostly due to drugs or maternal hyperthyroidism), or permanent. Genetic causes are listed in Table 1.

Defects of Thyroid Hormone Transport in Serum

For complete coverage of this and related areas visit the chapter entitled "Defects of thyroid hormone transport in serum" in the thyroid section of Endotext by Samuel Refetoff. Inherited abnormalities of the iodothyronine-binding serum proteins include TBG deficiency (partial or complete), TBG excess, transrethyretin (TTR) (prealbumin) variants, and familial dysalbuminemic hyperthyroxinemia (FDH). In these conditions the concentration of free hormones is unaltered, but the abnormal total thyroxine concentrations can be misleading during neonatal screening and in the evaluation of thyroid function.

Impaired Sensitivity to Thyroid Hormone

For complete coverage of this and related areas visit the chapter entitled: "Impaired sensitivity to thyroid hormone: defects of transpor**t,** metabolism and action" in the thyroid section of Endotext by Alexandra M. Dumitrescu and Samuel Refetoff. Impaired sensitivity to thyroid hormone includes defects in thyroid hormone action, transport, and metabolism. They are classified as a) thyroid hormone cell membrane transport defects, b) thyroid hormone metabolism defect, and c) thyroid hormone action defect that include resistance to thyroid hormone.

Causes of Transient Neonatal Hypothyroidism

Transient neonatal hypothyroidism should be distinguished from a 'false positive' result in which the screening result is abnormal but the confirmatory serum sample is normal. Causes of transient abnormalities of thyroid function in the newborn period are listed in Table 2. While iodine deficiency, iodine excess, drugs and maternal TSH receptor blocking antibodies are the most common causes of transient hypothyroidism, in some cases the cause is unknown.

TABLE 2. CAUSES OF TRANSIENT HYPOTHYROIDISM IN THE NEWBORN
PRIMARY HYPOTHYROIDISM
Prenatal or postnatal iodine deficiency or excess
Maternal antithyroid medication

Maternal TSH receptor blocking antibodies Mild gene mutations (i.e. DUOX2, TSH-R) Maternal hypothyroidism Prematurity, VLBW Drugs, (i.e. Dopamine, steroids) Hypothyroxinemia (low T4, normal TSH)
CENTRAL HYPOTHYROIDISM Prenatal exposure to maternal hyperthyroidism Prematurity (particularly <27 weeks gestation) Drugs

IODINE DEFICIENCY OR EXCESS

In addition to iodine deficiency, both the fetus and newborn infant are sensitive to the thyroid-suppressive effects of excess iodine, whether administered to the mother during pregnancy, lactation, or directly to the baby. This occurs because recovery from the thyroid-suppressive effect of iodine does not mature before 36 weeks gestation. Reported sources of iodine include drugs (e.g., potassium iodide, amiodarone), radiocontrast agents, and antiseptic solutions (e.g., povidone-iodine) used for skin cleansing or vaginal douches. In contrast to Europe, iodine-induced transient hypothyroidism has not been documented frequently in North America.

MATERNAL ANTITHYROID MEDICATION

Transient neonatal hypothyroidism may develop in babies whose mothers are being treated with antithyroid medication (either propylthiouracil, PTU or methimazole) for the treatment of Graves' disease. Even maternal PTU doses of 200 mg or less have been associated with an effect on neonatal thyroid function, illustrating the increased fetal sensitivity to these drugs. Babies with PTU- or methimazole-induced hypothyroidism characteristically develop an enlarged thyroid gland and if the dose is sufficiently large, respiratory embarrassment may occur. Both the hypothyroidism and goiter resolve spontaneously with clearance of the drug from the baby's circulation. Usually replacement therapy is not required.

MATERNAL TSH RECEPTOR ANTIBODIES

Maternal TSH receptor blocking antibodies, a population of antibodies closely related to the TSH receptor stimulating antibodies in Graves' disease, may be transmitted to the fetus in sufficient titer to cause transient neonatal hypothyroidism. The incidence of this disorder has been estimated to be 1 in 180,000. TSH receptor blocking antibodies most often are found in mothers who have been treated previously for Graves' disease or who have the non-goitrous form of chronic lymphocytic thyroiditis (primary myxedema). Occasionally these mothers are not aware that they are hypothyroid and the diagnosis is made in them only after CH has been recognized in their infants. Unlike TSH receptor stimulating antibodies that mimic the action of TSH, TSH receptor blocking antibodies inhibit both the binding and action of TSH. Because TSH-induced growth is blocked, these babies do not have a goiter. Similarly, inhibition of TSH-induced radioactive iodine uptake may result in a misdiagnosis of thyroid agenesis. Usually the hypothyroidism resolves in 3 or 4 months. Babies with TSH receptor blocking-antibody induced hypothyroidism are difficult to distinguish at birth from the more common thyroid dysgenesis but they differ from the latter in a number of important ways (Table

3). They do not require lifelong therapy, and there is a high recurrence rate in subsequent offspring due to the tendency of these antibodies to persist for many years in the maternal circulation. Unlike babies with thyroid dysgenesis in whom a normal cognitive outcome is found if postnatal therapy is early and adequate, babies with maternal blocking-antibody induced hypothyroidism may have a permanent deficit in intellectual development if feto-maternal hypothyroidism was present in utero.

TABLE 3. CLINICAL FEATURES OF THYROID DYSGENESIS VERSUS TSH RECEPTOR BLOCKING ANTIBODY INDUCED CONGENITAL HYPOTHYROIDISM

	Dysgenesis	**Blocking Ab**
Severity of CH	+ to ++++	+ to ++++
Palpable thyroid	No	No
123I uptake	None to low	None to normal
Clinical Course	Permanent	Transient
Familial risk	No	Yes
TPO Abs	Variable	Variable
TSH Receptor Abs	Absent	Potent

TRANSIENT CENTRAL HYPOTHYROIDISM DUE TO MATERNAL HYPERTHYROIDISM

Occasionally, babies born to mothers who were hyperthyroid during pregnancy develop transient hypothalamic-pituitary suppression. This hypothyroxinemia is usually self-limited, but in some cases, it may last for years and require replacement therapy. In general, the titer of TSH receptor stimulating antibodies in this population of infants is lower than in those who develop transient neonatal hyperthyroidism.

PREMATURITY

Hypothyroxinemia in the presence of a 'normal' TSH occurs most commonly in premature infants in whom it is found in 50% of babies of less than 30 weeks gestation. Often the free T4 when measured by equilibrium dialysis is less affected than the total T4. The reasons for the hypothyroxinemia of prematurity are complex. As well as hypothalamic-pituitary immaturity, premature infants frequently have TBG deficiency due to both immature liver function and undernutrition, and they may have "sick euthyroid syndrome". They may also be treated with drugs that suppress the hypothalamic-pituitary-thyroid axis. Hypothyroxinemia of prematurity may be associated with adverse neurodevelopmental outcomes. L-T4 treatment overall has no proven benefit and can be harmful. Long term outcome evaluation in young adults did not find an association between transient hypothyroxinemia of prematurity and neurodevelopmental outcome. Whether or not premature infants with hypothyroxinemia should be treated remains controversial at the present time. Although several retrospective, cohort studies have documented a relationship between severe hypothyroxinemia and both developmental delay and disabling cerebral palsy in preterm infants <32 weeks gestation a causal relationship could not be determined since the serum T4 in premature infants, as in adults, has been shown to reflect the severity of illness and risk of death.

DRUGS

Drugs that suppress the hypothalamic-pituitary axis

include known agents such as steroids and dopamine, but also aminophylline, caffeine and diamorphine, which are commonly used in sick premature infants.

Other Causes of Hypothyroidism in Infancy

CHRONIC LYMPHOCYTIC THYROIDITIS

Chronic lymphocytic thyroiditis (CLT) is a rare disease in infancy, but if not recognized and treated, can cause severe hypothyroidism with permanent brain damage. CLT can be associated with other autoimmune disease such as type 1 diabetes or as a manifestation of the IPEX syndrome. Clinical manifestations and biochemical hypothyroidism (TSH ranged from >42 to 928 mU/L) were severe and very high levels of antibodies were detectable.

IPEX RELATED DISORDERS

Lymphocytic thyroiditis has also been described in newborns with severe defects in tolerance and autoimmunity with immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, a polyglandular disorder characterized by early-onset diabetes and colitis. IPEX disorders are an expanding spectrum of disease with mutations in FOXP3, CD25 deficiency, STAT5 deficiency, and others.

HEPATIC HEMANGIOMAS: CONSUMPTIVE HYPOTHYROIDISM

Hepatic hemangioendothelioma is a rare tumor typically presenting in infancy. Hypothyroidism is caused by a production of type 3 deiodinase by the vascular tumor. D3 deiodinase increases inactivation of T4 and T3 to reverse T3 and T2 and a large amount of LT4 (up to 94/ µg/kg/day) is needed to compensate for this inactivation. Frequent monitoring is required, adapting the LT4 treatment to the growing proliferative phase of the tumor. Today hemangioendotheliomas in infancy may successfully being treated with steroids and propranolol and may undergo spontaneous regression. Some babies underwent liver transplantation.

SCREENING STRATEGIES

The aim of neonatal screening is the earliest identification of any form of CH, but particularly those patients with severe hypothyroidism in whom disability is greatest if not treated. The identification of Central CH by screening programs is under debate. Two screening strategies for the detection of CH have evolved. In the primary T4/backup TSH method, still favored in much of North America and the Netherlands, T4 is measured initially while TSH is checked on the same blood spot in those specimens in which the T4 concentration is low. In the primary TSH approach, favored in most parts of Europe and Japan, blood TSH is measured initially.

A primary T4/backup TSH program will detect overt primary hypothyroidism, secondary or tertiary hypothyroidism, babies with a low serum T4 level but delayed rise in the TSH concentration, TBG deficiency and hypothyroxinemia; this approach may, however, miss subclinical hypothyroidism. A primary TSH strategy, on the other hand, will detect both overt and subclinical hypothyroidism, but will miss secondary or tertiary hypothyroidism, a delayed TSH rise, TBG deficiency and hypothyroxinemia. There are fewer false positives with a primary TSH strategy. Both programs will miss the rare infant whose T4 level on initial screening is normal but who later develops low T4 and elevated TSH concentrations. This pattern has been termed “atypical” CH or “delayed TSH” and is observed most commonly in premature babies with transient hypothyroidism or infants with less severe forms of permanent disease.

According to the European Society for Pediatric Endocrinology (ESPE) guidelines, the most sensitive test for detecting primary CH is the determination of TSH concentration that detects primary CH more effectively than primary T4 screening Primary T4 screening with confirmatory TSH testing can detect some cases of central CH, but some cases of mild CH can be missed, depending on the cutoff T4 value used.

Measurement of T4 and/or TSH is performed on an eluate of dried whole blood (DBS) collected on filter paper by skin puncture on day 1-4 of life. Primary CH screening has been shown to be effective for the testing of cord blood or the blood collected on filter paper after the age of 24 hours. Blood is applied directly to the filter paper and after drying the card is sent to the laboratory. The best time to collect blood for TSH screening is 48 to 72 hours of age. The practice of early discharge from the hospital of otherwise healthy full-term infants has resulted in a greater proportion of babies being tested before this time. For example, it has been estimated that in North America 25% or more of newborns are now discharged within 24 hours of delivery and 40% in the second 24 hours of life. Because of the neonatal TSH surge and the dynamic changes in serum T4 and T3 concentrations that occur within the first few days of life, early discharge increases the number of false positive results. It is important that in the screening laboratory the results of TSH are interpreted in relation to time of sampling.

Physicians caring for infants need to appreciate that there is always the possibility for human error in failing to identify affected infants, whichever screening program is utilized. This can occur due to poor communication, lack of receipt of requested specimens, or the failure to test an infant who is transferred between hospitals during the neonatal period. Therefore, if the diagnosis of hypothyroidism is suspected clinically, the infant should always be tested. Adult normative values, provided by many general hospital laboratories, differ from those in the newborn period and should never be employed.

Special categories of neonates with CH can be missed at screening performed at the usual time, particularly preterm babies and neonates with serious illnesses and multiple births. Drugs used in neonatal intensive care (i.e., dopamine, glucocorticoids that suppresses TSH), immaturity of hypothalamic-pituitary thyroid axis, decreased hepatic production of thyroid binding globulin, reduced transfer of maternal T4, reduced intake of iodine or excess iodine exposure, fetal blood mixing in multiple births can affect the first sample, and in many centers a second specimen is required to rule out CH. Preterm babies have a higher incidence of a unique form of hypothyroidism, characterized by a delayed elevation of TSH. These babies can later develop low T4 and elevated TSH concentrations. This pattern has been termed “atypical” CH or “delayed TSH”. Preterm babies with a birth weight of less than 1500 gr. have an incidence of CH of 1:300. Survival of even extremely premature babies (<28 weeks of gestation) is around 90% in developed countries, and the incidence of prematurity is around 11.5 % in US and 11.8 % worldwide. So, an increasing subpopulation of preterm babies and high-risk newborns deserves a special screening and follow up for CH.

In these categories a second specimen 2-6 weeks from the first (ESPE guidelines suggested at about 15 days, or after 15 days from the first) may be indicated in a) preterm neonates with a gestational age of less than 37 weeks, b) Low Birth Weight and Very Low Birth Weight neonates, c) ill and preterm neonates admitted to neonatal intensive care unit, d) if specimen collection was within the first 24 hours of life, and e) multiple births, particularly in the case of same sex twins. The interpretation of the screening results should consider the results of a multiple sampling

strategy, the age of sampling, and the maturity (GA/birth weight) of the neonate. A second screen (using a lower TSH cutoff) is able to detect the delayed elevation of TSH that occurs in these babies.

CH is defined on the basis of serum FT4 levels as severe when FT4 is <5 pmol/l, moderate when FT4 is 5 to 10 pmol/l, and mild when FT4 is 10 to 15 pmol/l, respectively. Determination of serum thyroglobulin (Tg) is useful, if below the detection threshold, to suggest athyreosis or a complete thyroglobulin synthesis defect. Measurement of Tg is most helpful when a defect in Tg synthesis or secretion is being considered. In the latter condition the serum Tg concentration is low or undetectable despite the presence of a normal or enlarged, eutopic thyroid gland. Serum Tg concentration also reflects the amount of thyroid tissue present and the degree of stimulation. For example, Tg is undetectable in most patients with thyroid agenesis, intermediate in babies with an ectopic thyroid gland, and may be elevated in patients with abnormalities of thyroid hormonogenesis not involving Tg synthesis and secretion. Considerable overlap exists, and so, the Tg value needs to be considered in association with the findings on imaging. In patients with inactivating mutations of the TSH receptor discordance between findings on thyroid imaging and the serum Tg concentration has been described in some but not all studies.

IMAGING TECHINIQUES IN CH

Imaging studies are helpful to determine the specific etiology of CH. Both scintigraphy and ultrasound (US) should be considered in neonates with high TSH concentrations. Ideally, the association of US and scintigraphy gives the best information in a child with primary hypothyroidism. Scintigraphy shows the presence/absence (athyreosis), position (ectopic gland, in any point from the foramen caecum at the base of the tongue to the anterior mediastinum) and rough anatomic structure of the thyroid gland. US, is a useful tool in defining size and morphology of a eutopic thyroid gland, however, US alone is less effective in detecting ectopic glands. Color Doppler US improves the effectiveness of US. It is important to remember that an attempt to obtain imaging in a newborn should never delay the initiation of treatment. Scintigraphy should be carried out within 7 days of starting LT4 treatment. Scintigraphy may be carried out with either 10-20 MBq of technetium ^{99}m (^{99}mTc) or 1-2 MBq of iodine^{123} (I^{123}). Tc is more widely available, less expensive, and quicker to use than I^{123}. Scintigraphy with I^{123}, if available, is usually preferred because of the greater sensitivity and because, I^{123}, unlike of technetium^{99}, is organified. Therefore, imaging with this isotope allows quantitative uptake measurements and tests for both iodine transport defects and abnormalities in thyroid oxidation. An enrichment of the tracer within the salivary gland can lead to misinterpretation, especially on lateral views, but this can be avoided by allowing the infant to feed before scintigraphy, thus empting the salivary glands and keeping the child calm under the camera. The perchlorate discharge test is considered indicative of an organification defect when a discharge of > 10% of the administered I^{123} dose occurs in a thyroid in normal position (when perchlorate is given at 2 hours).

Excess iodine intake through exposure, maternal TSH receptor blocking antibodies, inactivating mutation in the TSH receptor and in the sodium/iodide symporter (NIS), and TSH suppression from LT4 treatment can interfere with the I^{123} uptake, showing no uptake in the presence of a thyroid in situ (apparent athyreosis).

Thyroid ultrasonography is performed with a high frequency linear array transducer (10-15 MHz) and allows a resolution of 0.7 to 1mm. Thyroid tissue is more echogenic than muscle and less echogenic than

fat. In the case of absence of the thyroid, fat tissue can be misdiagnosed as dysplastic thyroid gland in situ. Distinguishing between thyroid hypoplasia and dysplastic non-thyroidal tissue in a newborn requires an experience and reevaluation at a later age can result in a different diagnosis.

Combining scintigraphy and thyroid ultrasound improves diagnostic accuracy and helps to address further investigations, including molecular genetic studies. Infants found to have a normal sized gland in situ in the absence of a clear diagnosis should undergo further reassessment of the thyroid axis and imaging at a later age.

THERAPY

Timing of normalization of thyroid hormones is critical for brain development and therefore replacement therapy with L-thyroxine (L-T4) should be begun as soon as the diagnosis of CH is confirmed. Treatment should be started immediately if DBS TSH concentration is >40 mUI/l because this value strongly suggests decompensated hypothyroidism. If TSH is < 40 mUI/l the clinician may postpone treatment, pending the serum results, for 1-2 days. ESPE guidelines suggest treatment should be started if venous TSH concentration is persistently >20 mUI/l, even if serum FT4 is normal. Severe hypothyroidism is defined by T4 <5 mcg/dL (64 nmol/L) and/or TSH >40 mU. According to ESPE guidelines, CH is defined on the basis of serum FT4 levels as severe when FT4 is <5 pmol/l, moderate when FT4 is 5 to 10 pmol/l, and mild when FT4 is 10 to 15 pmol/l. As noted above, treatment need not be delayed in anticipation of performing thyroid imaging studies as long as the latter are done within 5-7 days of initiating treatment (before suppression of the serum TSH). Parents should be counseled regarding the causes of CH, the importance of compliance, and the excellent prognosis in most babies if therapy is initiated sufficiently early and is adequate. Educational materials should be provided. An initial dosage of 10-15 mcg/kg/day of L-T4 is generally recommended to normalize the T4 as soon as possible. The highest dose is indicated in infants with severe disease, and the lower dose in those with a mild to moderate CH. L-T4 tablets can be crushed and given via a small spoon, with suspension, if necessary in a few milliliters of water or breast milk or formula or juice, but care should be taken that all of the medicine has been swallowed. Thyroid hormone should not be given with substances that interfere with its absorption, such as iron, calcium, soy, or fiber. Drugs such as antacids (aluminum hydroxide) or infantile colic drops (simethicone) can interfere with L-thyroxine absorption. Many babies will swallow the pills whole or will chew the tablets with their gums even before they have teeth. Reliable liquid preparations are not available commercially in the US, although they have been used successfully in Europe. A brand name rather a generic formulation of L-T4 is recommended because they are not bioequivalent.

It is still a matter of debate if treatment can be beneficial in otherwise healthy babies with venous TSH concentration between 6-20 mUI/l and FT4 concentration within the normal limits for age. In these cases, diagnostic imaging is recommended to try to establish a definitive diagnosis. If TSH concentration remains high for more than 3 or 4 weeks, it is possible (in discussion with the family) to either start LT4 supplementation immediately and then retest off treatment at a later stage or retest two weeks later without treatment. Given the irreversibility of possible harm, treating during early childhood and revaluating thyroid function after myelination of the central nervous system is completed (by 36 to 40 months of age) can be a prudent approach. LT4 treatment must be started immediately if FT4 or TT4 levels are low, given the known adverse effect of untreated

decompensated CH on neurodevelopment and somatic growth.

The aims of therapy are to normalize the T4 as soon as possible, to avoid hyperthyroidism where possible, and to promote normal growth and development. When an initial dosage of 10-15 mcg/kg is used, the T4 will normalize in most infants within 1 week and the TSH will normalize within 1-month. Subsequent adjustments in the dosage of medication are made according to the results of thyroid function tests and the clinical picture. Often small increments or decrements of L-thyroxine (12.5 mcg) are needed. This can be accomplished by 1/2 tablet changes, by giving an alternating dosage on subsequent days, or by giving an extra tablet once a week.

As stated in ESPE guidelines: "L-T4 alone is recommended as the medication of choice and should be started as soon as possible, no later than two weeks of life or immediately after confirmatory test results in infants identified in a second routine screening test. L-T4 should be given orally. If intravenous administration is necessary, the dose should be no more than 80% of the oral dose". Serum or plasma FT4 (or TT4) and TSH concentration should be determined at least 4 hours after the last L-T4 administration. TSH should be maintained in the age-specific reference range and FT4 in the upper half of the age- specific reference range. "The first follow up examination is indicated after 1-2 weeks after the start of LT4 treatment and then every 2 weeks until TSH levels are completely normalized and then every 1- 3 months until 12 months of age. Between the age of one and three years, children should undergo frequent clinical and laboratory evaluations (every 2 to 4 months)." Thereafter, evaluations should be carried out every 3 to 12 months until growth is completed. "More frequent evaluations should be carried out if compliance is questioned or abnormal values are obtained. Any reduction of L-T4 dose should not be based on a single increase of FT4 concentration during treatment. "Measurements should be performed after 4-6 weeks any change in the dosage or in the L-T4 formulation".

RE-EVALUATION AND TRIAL OFF THERAPY

In hypothyroid babies in whom an organic basis was not established at birth and in whom transient disease is suspected, a trial off replacement therapy can be initiated after the age of 3 years when most thyroxine-dependent brain maturation has occurred, as shown by MRI studies. Re-evaluation is recommended if the treatment was started in a sick child (i.e. preterm), if thyroid antibodies were detectable, if no diagnostic assessment was completed, and in children who have required no increase in L-T4 dosage since infancy. Re-evaluation is recommended also in the case of a eutopic gland with or without goiter, if no enzyme defects have been detected, or if any other cause of transient hypothyroidism is suspected.

Re-evaluation is not necessary if venous TSH concentration has risen during the first year of life, due to either LT4 underdosage or poor compliance. To perform a precise diagnosis, LT4 treatment is suspended for 4-6 weeks, and biochemical testing and thyroid imaging are carried out. To establish the presence of primary hypothyroidism, without defining the cause, L-T4 dose may be decreased by 20-30% for 2 to 3 weeks. If TSH serum levels rise to > 10 mU/L during this period, the hypothyroidism can be confirmed.

PROGNOSIS

Although all agree that the mental retardation associated with untreated CH has been largely eradicated by newborn screening, controversy

persists as to whether subtle cognitive and behavioral deficits remain, particularly in the most severely affected infants. Both the initial treatment dose and early onset of treatment (before 2 weeks) are important. Time to normalization of circulating thyroid hormone levels, the initial free T4 concentration, maternal IQ, socioeconomic status, and ethnic status have also been related to outcome. The long-term problems for these babies appear to be in the areas of memory, language, fine motor, attention, and visual spatial. Inattentiveness can occur both in patients who are overtreated and those in whom treatment was initiated late or was inadequate. In addition to adequate dosage, assurance of compliance and careful long-term monitoring are essential for an optimal developmental outcome. More details about long term follow up are reported in ESPE guidelines. Progressive hearing loss in CH should be recognized and corrected, because they strongly influenced the outcome.

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