Congenital hypothyroidism: recommendations of the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism

Hipotireoidismo congênito: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia

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ABSTRACT

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder, with an incidence of 1:2,000 to 1:4,000 live births and it is a leading preventable mental retardation. Neonatal Screening Programs allow early identification of the disease and the adequate treatment of affected children can avoid the complications related to deprivation of the hormone. Most cases of primary congenital hypothyroidism (85%) are due to thyroid dysgenesis (ectopia, hypoplasia or agenesis) while the remaining result from defects in hormone synthesis. Affected children (> 95%) usually have no symptoms suggesting the disease at birth. The most frequent symptoms and signs are prolonged neonatal jaundice, hoarse cry, lethargy, slow movements, constipation, macroglossia, umbilical hernia, large fontanelle, hypotonia and dry skin. Around the world, various strategies are used for the screening of the CH. In Brazil, screening for CH is mandatory by law and usually done by serum TSH in dried blood collected from the heel. The recommended age for performing this test is after 48 hours of life until the 4th day. Diagnostic confirmation is required dosing TSH and free T_4 or total T_4 in serum. Arq Bras Endocrinol Metab. 2013;57(3):184-92

Keywords
Congenital hypothyroidism; neonatal screening

RESUMO

O hipotireoidismo congênito (HC) é o distúrbio endócrino congênito mais frequente, com incidência variando de 1:2.000 a 1:4.000 crianças nascidas vivas e uma das principais causas de retardo mental que pode ser prevenida. Os Programas de Triagem Neonatal para a doença permitem a identificação precoce dos afetados e seu tratamento de modo a evitar as complicações da falta do hormônio. A maioria dos casos de hipotireoidismo congênito é decorrente de disgenesias tireoidianas (85%), entre elas a ectopia, hipoplasia ou agenesia tireoidianas, e os demais resultam de defeitos de síntese hormonal. As crianças afetadas (> 95%) geralmente não apresentam sintomas sugestivos da doença ao nascimento. Os sintomas e sinais mais comuns são: icterícia neonatal prolongada, choro rouco, letargia, movimentos lentos, constipação, macroglossia, hérnia umbilical, fontanelas amplas, hipotonia e pele seca. Várias estratégias são utilizadas para a triagem do HC. No Brasil, esta é obrigatória por lei e geralmente é feita com a dosagem de TSH em sangue seco coletado do calcanhar. A idade recomendada para sua realização é após as 48 horas de vida até o quarto dia. A confirmação diagnóstica é obrigatória com as dosagens de TSH e T_4 livre ou T_4 total. Arq Bras Endocrinol Metab. 2013;57(3):184-92

Descritores
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INTRODUCTION

Congenital hypothyroidism (CH) is the most common congenital endocrine disorders, with an incidence of 1:2,000 to 1:4,000 live births in iodine-sufficient countries (1,2) (**B**). In Brazil, the incidence of CH is close to these values, ranging from 1:2,595 to 1:4,795 (3,4) (**B**). However, recent studies indicate a higher incidence of CH in the United States, from 1:4,094 in 1987 to 1:2,372 in 2002 (5) (**B**). This higher incidence may be due to improved means of detecting subclinical cases of the disease as a consequence of a lower cutoff point for thyroid stimulating hormone (TSH) levels and the inclusion of transient hypothyroidism in the screening process (6-9) (**D**).

The prevalence of CH varies among ethnic groups and is significantly less prevalent among African Americans compared to Hispanics (1:10,000 *vs.* 1:2,700). Regarding gender, CH is more prevalent in females (2:1). In addition, children with Down syndrome have a 35-fold increased risk of CH compared to the general population (10) (**B**).

In the absence of early diagnosis and proper treatment, most children develop varying degrees of neurological, motor and growth deficits, including irreversible mental retardation.

METHODS

Active searches were conducted in the primary databases Medline and SciELO using the following keywords (MeSH Terms): congenital hypothyroidism and neonatal screening.

Grade of recommendation and strength of evidence

The strength of evidence was evaluated according to the Oxford classification system and established based on the experimental design used, considering the best available evidence for each question and the Brazilian experience.

A: Most consistent experimental and/or observational studies.

B: Less consistent experimental and/or observational studies.

C: Case reports.

D: Opinion without critical evaluation based on consensus, physiological studies or animal models.

1. WHAT ARE THE CAUSES OF CH?

The most frequent cause of permanent CH is thyroid dysgenesis, which results from defects in glandular formation during embryogenesis, and represents 85% of the cases (Table 1). This group encompasses thyroid ectopy, agenesis and hypoplasia, which account for 30%-45%, 35%-45% and 5% of cases, respectively (11) (**D**). The precise reasons for these alterations remain unclear, although mutations in transcriptional factors that regulate thyroid gland development, such as thyroid transcription factor 2 (*TTF-2*), *NKX2.1* (also known as *TTF-1*) and paired box gene 8 (*PAX-8*) have been reported to be involved. However, only 2% of dysgenesis cases exhibit these genetic mutations (12) (**B**). These transcriptional factors are present in other tissues and are associated with CH syndrome. Thus, mutations in *NKX2.1*, a gene that participates in lung and brain development, cause neonatal respiratory distress and choreoathetosis in the newborn (NB). Patients with mutations in *TTF-2* present with spiky hair, cleft palate, anal atresia and thyroid agenesis (11) (**D**).

Other etiologies of permanent CH are defects in hormone production called dyshormonogenesis that represent approximately 15% of cases. The defects are autosomal recessive and include mutations in genes encoding the sodium-iodide symporter (NIS) (*SLC5A5* gene), thyroperoxidase (TPO), hydrogen peroxide generation factors [thyroid oxidase and dual oxidase maturation factors (*DUOXA1* and *DUOX2* genes)], thyroglobulin (Tg) and iodothyronine deiodinases (13).

Uncommon causes of CH include defects in thyroid hormone (TH) transport, such as mutations in the monocarboxylase transporter 8 (*MCT8*) gene (14) (**C**); resistance to TH (syndrome of resistance to thyroid hormone) (15) (**D**), resistance to TSH (16) (**C**) and central hypothyroidism (17,18) (**B**).

Central hypothyroidism can be due to isolated TSH deficiency or, more commonly, hypopituitarism, which causes deficiency in several adenohypophysis hormones. Mutations in many genes involved in pituitary development or function have been implicated, including *HESX1*, *LHX4*, *PIT-1* and *PROP1*. Resistance to thyrotropin-releasing hormone (TRH) due to a mutation in the gene encoding the TRH receptor may also cause central hypothyroidism (18).

Resistance to thyroid hormone syndrome is a rare disorder with a variable clinical spectrum that depends on the level of TH hyporesponsiveness.

Resistance to TSH is defined as elevated serum TSH concentrations (hyperthyrotropinemia) in the absence of goiter. Affected individuals have normal or hypoplastic thyroid glands and their serum T_4 and T_3 values are normal or low.

Defects in TH transport caused by mutations in the *MCT8* gene, which is located on the X chromosome, impairs T_3 transport and leads to mental retardation. The syndrome is characterized by high serum T_3, low serum T_4 and high serum TSH concentrations.

Recommendation 1

The most frequent cause of permanent CH is thyroid dysgenesis, which includes thyroid agenesis, ectopy and hypoplasia (B). Dyshormonogenesis is the second most common cause (B). Rare causes of CH include central hypothyroidism (B), syndrome of resistance to thyroid hormone (D), TSH resistance syndrome (C) and *MCT8* mutations (C).

2. CAN CH BE TRANSIENT?

CH can be transient and can result from several causes:

- Excessive (or deficient) iodine intake by the mother.
- Maternal anti-thyroid drugs intake (mothers with hyperthyroidism).
- Transplacental passage of maternal antibodies that block the TSH receptor. This diagnosis should be considered when the mother reports the occurrence of more than one child with transient hypothyroidism detected by neonatal screening. It usually lasts 1-3 months, i.e., until the antibodies disappear from circulation.
- Heterozygous mutations in enzymes DUOX1 (*DUOXA1* gene) or DUOX2/THOX (*DUOX2* gene).
- Large liver hemangiomas (increased deiodinase type 3 activity) (7,8) (**D**).

Patients classified as having HC due to synthesis defects were followed for 3 years and, at re-evaluation, only 47% had permanent hypothyroidism. Thus, it is recommended to evaluate all children with topic thyroid at age of 3 to define the presence or absence of the disease (19) (**B**).

Recommendation 2

Neonatal hypothyroidism may be permanent or transient. It is recommended that children be re-evaluated at 3 years of age; for patients with unclear hypothyroidism etiology, levothyroxine (L-T4) treatment should be discontinued (B).

3. CLINICAL MANIFESTATIONS OF CH

Most children with CH (> 95%) have little or no clinical manifestation of the disease at birth (20) (**B**) due to the transplacental passage of maternal T_4 (21) (**B**) and because most affected children have some functioning thyroid tissue. As TH has a half-life of 7 days, the maternal hormone is metabolized and excreted approximately 3-4 weeks after birth.

Affected children typically present normal weight and height. One of the first signs is prolonged neonatal jaundice (22,23) (B). Over time, undiagnosed children appear lethargic, with slow movements, hoarse cry, feeding difficulties, constipation, macroglossia, umbilical hernia, large anterior or posterior fontanels, hypotonia, dry skin, thinning hair and typical facies with saddle nose. Some NBs with dyshormonogenesis present with a palpable goiter at birth, but this condition may also appear later, even with treatment (23). An x-ray of knee epiphyses may reveal delayed ossification, which reflects fetal hypothyroidism severity. Table 2 lists symptoms or

Table 1. Main etiologies of CH and hormonal changes

Etiology	Incidence	TSH	Free T_4	Total T_4
Primary hypothyroidism	1:2,000-1:4,000			
Dysgenesis (ectopy, hypoplasia, agenesis)	85% of cases	Increased	Decreased	Decreased
Dyshormonogenesis	15% of cases			
Central hypothyroidism	1:50,000-1:100,000	Decreased, normal or slightly Increased	Decreased	Decreased
Transient hypothyroidism				
Iodine deficiency	1:100 – Europe	Increased with later normalization	Decreased with later normalization	Decreased with later normalization
Excess iodine	1:50,000 – USA			
Passage of maternal antibodies	1:25,000-1:100,000			

signs exhibited in affected children according to disease severity (24) (**B**). Screening of Brazilian newborns with CH was associated with umbilical hernia (48.9%), saddle nose (46.6%), prolonged jaundice beyond 7 days (44.4%) and 20% of cases had no clinical manifestation (25) (**A**).

When the etiologic diagnosis of CH is hypopituitarism, the child will be predisposed to hypoglycemia due to growth hormone and adrenocorticotropic hormone (ACTH)/cortisol deficiency, and males will exhibit micropenis. These children are at risk of death if the disease is not detected early, and it is usually not detected by NB screening utilizing TSH measurement.

Table 2. Occurrence of symptoms and signs of CH at the time of diagnosis according to disease severity

	Total T_4 < 2.5 µg/dL n = 215 (%)	Total T_4 > 2.5 µg/dL n = 232 (%)
Prolonged jaundice	128 (59)	77 (33)**
Feeding difficulty	75 (35)	36 (16)**
Lethargy	73 (34)	32 (14)**
Umbilical hernia	68 (32)	42 (18)*
Macroglossia	53 (25)	28 (12)*
Constipation	38 (18)	24 (10)
Cold skin	39 (18)	24 (10)
Hoarse cry	16 (7)	15 (6)
Hypothyroid appearance	12 (6)	6 (2)
Hypothermia	6 (3)	7 (3)
Hypotonia	6 (3)	7 (3)
No symptoms	34 (16)	78 (33)**

* $p < 0.01$; ** $p < 0.001$.
Modified from Grant and cols., 1992 (24) (**B**).

Recommendation 3

Despite the possibility of the absence of clinical symptoms in infants with congenital hypothyroidism, the signs and symptoms described in table 2 should serve as a warning (B).

4. CAN CH OCCUR IN ASSOCIATION WITH CONGENITAL ABNORMALITIES?

Children with CH have an additional risk of malformations (10% *vs.* 3% in normal children) mainly affecting the heart (4-fold increased risk) but also the kidneys, urinary tract and gastrointestinal and skeletal systems (26,27) (**B**).

Children with CH and cleft palate may have mutations in TTF-2 (*FOXE-1* gene) (28) (**C**), and those with persistent neurological symptoms, including ataxia, may have mutations in the *NKX2.1* gene (29) (**C**).

Hearing problems occur in approximately 20% of children with CH, and all affected children should undergo a hearing screening test (30,31) (**B**).

There is no consensus for conducting screening tests for congenital anomalies. However, a careful physical examination is important, and the child should be referred for evaluation if any alteration is detected.

The early detection of other malformations in patients with CH may modify the prognosis of these patients (32) (**B**).

Recommendation 4

Hearing screening and a careful physical examination are recommended to search for other congenital abnormalities in children with congenital hypothyroidism (**B**).

5. IS NB SCREENING EFFECTIVE FOR TRACKING EARLY HYPOTHYROIDISM?

The main purpose of NB screening for CH is to avoid sequelae, especially hypothyroidism-induced mental retardation, which can be achieved initiating therapy within the first 2 weeks of life (33) (**B**).

Neonatal screening for CH is routine in the United States, Canada, Europe, Israel, Japan, Australia and New Zealand, and it is in development in Eastern Europe, South America, Asia and Africa.

The high sensitivity of NB screening tests for CH makes them an effective way to identify disease. Population studies conducted in Europe and the United States have reported sensitivities of 97-100% and specificities of 98%-100% (34,35) (**A**).

Recommendation 5

Neonatal screening is recommended to track CH (A).

6. WHEN SHOULD NB SCREENING TESTS FOR HYPOTHYROIDISM BE PERFORMED?

For the NB screening test, blood is collected from the heel and placed on filter paper, which is added to a card that lists the child's data (date of birth, gestational age, sex, weight, whether there was a blood transfusion etc.)

and contact information. It is recommended that blood collection be performed after 48 hours of birth to 4 days of life (36), when the physiological postnatal TSH peak has decreased. Ideally, the blood samples should be collected prior to hospital discharge; however, blood collection performed at early discharge (< 48 hours) may result in a false-positive result. In critically ill or preterm children, blood collection should be performed at 7 days of life; however, it is important to note that it may be too late for children with congenital adrenal hyperplasia or metabolic disease when blood samples are collected after 4 days of life (36). Due to the immaturity of the hypothalamic-pituitary-thyroid axis in preterm infants, some authors recommend repeating their screening test within 2 to 4 weeks of age.

When there is need for whole blood transfusion, heel blood should be collected before the child is transfused, regardless of age (37) (**D**).

Recommendation 6

Blood should be collected from NBs for screening after 48 hours of birth to 4 days of life or before the NB leaves the hospital and always before blood transfusion (**D**).

7. WHICH TESTS ARE PERFORMED IN BRAZIL TO SCREEN FOR CH?

There are several strategies to screen for CH:

1. TSH measurement.
2. Simultaneous measurement of TSH and T_4.
3. Initial measurement of T_4 followed by TSH if T_4 is below a certain limit (usually below the 10th percentile).

In Brazil, the public system performs TSH screening (TSHneo), with cutoff TSHneo values ranging from 5-20 µU/ml. Children with high TSHneo values are called for evaluation and confirmation.

The dosage of TSH has greater specificity than an isolated T4 dosage. The simultaneous dosage of TSH and T4 has higher sensitivity in all protocols, but also leads to a higher number of false positives (38) (**B**).

In some neonatal screening centers, children with TSHneo values between 10-20 µU/ml are recalled for a second collection onto filter paper, and if TSH is above 10 µU/ml, the results need to be confirmed in serum.

When only TSH is evaluated, children with central hypothyroidism or delayed TSH elevation may not be identified. Late TSH elevations are particularly common in children with low birth weight (< 2,500 g) and in preterm births (39) (**B**).

Screening with initial measurement of T_4 followed by TSH can detect cases of primary hypothyroidism, as well as central hypothyroidism and children with deficiency of thyroid hormone carrier protein (TBG). The latter group exhibits low total T_4 (TT_4) and normal free T_4 (FT_4) and will not require CH treatment. However, this approach will not detect children with CH that have normal T_4 due to less severe thyroid dysfunction. A comparison between the two approaches that involve TSH and T_4 measurements in different sequences showed that 1 in 93,000 screened children would not be diagnosed with the initial approach with T_4, which would not occur if TSH was evaluated first (40) (**B**).

Recommendation 7

In Brazil, NB screening for CH is performed by TSH determination on filter paper, followed by total T_4 and/or free T_4 measurement in serum, when necessary. This strategy is effective and has also been adopted in other countries (**A**).

8. SHOULD ABNORMAL SCREENING TEST RESULTS BE CONFIRMED?

NB screening tests for CH are not diagnostic, and abnormal results should be confirmed by quantitative methods to measure serum TSH and TT_4 or FT_4 (41) (**B**). Most confirmatory tests should be performed between the first and second weeks of life, when the upper level of the TSH normal range drops to 10 µU/ml. It should be noted that the normal range is different from that observed in adults. Between 4 to 30 days of life, the normal ranges of TT_4 and FT_4 are 7-16 µg/dL and 0.8-2.3 ng/dL, respectively (42).

TSH levels above 10 µU/mL and low FT_4 or TT_4 values confirm the diagnosis of primary hypothyroidism, and these children should undergo appropriate treatment (36).

Children with confirmatory TSH between 6-10 µU/ml and normal TT_4/FT_4 should be followed carefully, and these measurements should be repeated one week later. If slightly elevated TSH persists during the

first month of life, even with T_4 in the normal range, some researchers suggest treatment and re-evaluation at 3 years of age (19,43) (**B,D**).

Preterm infants and infants that are ill for any reason (euthyroid sick syndrome) may have low TT_4/FT_4 with normal TSH levels, and treatment with L-T4 is not recommended unless there is evidence of hypothalamic or pituitary disease (44).

Recommendation 8

Screening tests for CH that yield abnormal results should be confirmed by quantitative measurement of venous TSH and total T_4/free T_4 (B).

9. IDENTIFICATION OF HYPOTHYROIDISM ETIOLOGY

If the diagnosis of hypothyroidism is confirmed, further studies are necessary to determine the disease etiology; however, the decision to treat the disease is based on hormone levels, and additional tests are optional and should not delay the beginning of treatment.

Tests that may be required to elucidate CH etiology are as follows:

- Cervical ultrasonography – the main initial examination. Once the thyroid is located, the most common etiologies of agenesis and ectopy would be ruled out. However, ultrasonography is less sensitive than thyroid scintigraphy for detection of ectopic gland, even though Doppler ultrasound can successfully identify 90% of ectopic glands (45). The ultrasound has a sensitivity and specificity of 90.5% and 47.8%, respectively, for the diagnosis of agenesis and 100% and 80.4%, respectively, for hypoplasia, but has low sensitivity for the diagnosis of ectopy (only 10%) (46) (**B**). The advantages are to avoid exposure to radiation and lower cost (47) (**B**).
- Mapping with ^{99m}Tc – indicated when ultrasound does not detect the ectopic gland. Scintigraphy can be performed with technetium (^{99m}Tc) pertechnetate or iodine (^{123}I) instead of ^{131}I due to lower irradiation. Goiter can be observed when there is an enzyme defect. For detection of ectopic gland, it has a sensitivity and specificity of 92% and 97.1% respectively (46) (**B**).
- Thyroglobulin measurement – there is a large overlap of Tg values for different CH etiologies; therefore, Tg values are used only in special situations. The association between Tg levels and ultrasonography can distinguish between *athyreosis* and *ectopic glandular tissue*. Some functional ectopic tissue is present if no thyroid tissue is visualized in the normal location but T_4 and Tg levels are measurable (36,42).
- Measurement of antithyroid antibodies [anti-peroxidase (TPO) antibody and antibody that blocks TSH receptor (TRAb)] – this test may be useful to justify the presence of elevated TSH in the infants of mothers that have Hashimoto's thyroiditis (transient hypothyroidism) or Graves' disease (36).
- Urinary iodine – can confirm the lack or excess of iodine in suspected cases, and treatment with L-T4 should be established for several months until be gradually reduced.

Recommendation 9

Complementary investigations are necessary to determine the etiology of congenital hypothyroidism (B), but should never delay the start of treatment.

10. WHEN SHOULD TREAMENT BEGIN?

The age of treatment onset, the L-T4 dose administered and appropriate monitoring are essential for brain development of CH patients. There is an inverse relationship between the age of diagnosis/treatment and intelligence quotient (IQ). Children that are identified in NB screening programs and treated in the first weeks of life usually have a normal IQ, although some studies have shown that they also have cognitive deficits (48,49).

Recommendation 10

The beginning of the treatment should be as early as possible, preferably within the first 2 weeks of life (B).

11. DOES SODIUM L-T4 THERAPY NORMALIZE HORMONE LEVELS OF CHILDREN WITH CH?

Oral administration of sodium L-T4 is the treatment of choice for CH. The dose recommended by the American Academy of Pediatrics is 10-15 µg/kg/day, which should be initiated as early as possible, ideally within 14 days of life, even in the absence of symptoms (36)

(**D**). Studies show that with these doses, FT_4 or TT_4 and TSH concentrations normalize in 3 days and 2-4 weeks, respectively (50) (**A**).

L-T4 tablets should be used because the liquid form of the hormone is not approved for clinical use. The tablet should be crushed and dissolved in a small amount of water and administered in the morning, ideally while fasting. Food should be avoided for 30 minutes. In case of immediate vomiting, the same dose should be repeated. With good oral absorption and a half-life of approximately 7 days, L-T4 is administered daily (36) (**D**). Although it is recommended that L-T4 be given on an empty stomach and food should be avoided for 30-60 minutes, this is not practical in infants. Thus, L-T4 may be administered between feedings, and doses should be adjusted based on serum hormone levels. L-T4 cannot be used with other substances that interfere with its absorption, such as soybeans, iron or calcium.

Recommendation 11

CH treatment should be initiated as soon as possible, preferably within the first 15 days of life. Oral L-T4 is recommended at the initial dose of 10-15 µg/kg/day (**A**).

12. HOW SHOULD TREATMENT BE MONITORED?

Brain development is highly dependent on thyroid hormone levels for the first 2-3 years of life. There are studies showing that persistently low serum T_4 concentrations (TT_4 below 10 µU/ml) in the first year of life are associated with IQ approximately 18 points lower than the average IQ (51). The recommendations of the American Academy of Pediatrics (36) (**D**) regarding the treatment and monitoring of children are listed in table 3 (43).

More frequent laboratory testing may be necessary when there is poor compliance with the treatment, abnormal values are obtained or the dosage has been changed.

The goal of treatment is to ensure that the children have adequate growth and psychomotor development as close as possible to their genetic potential.

Care must be taken to avoid excessive treatment for prolonged periods, which may lead to craniosynostosis and changes in the child's temperament (51).

Table 3. CH treatment, monitoring and target hormone concentrations

Starting L-T4 dose	10-15 µg/kg/day
Monitoring free T_4 or total T_4 and TSH	At 2 and 4 weeks after indication of L-T4 treatment Every 1-2 months during the first months Every 2-3 months from 6-36 months Every 6-12 months until growth is complete
Target values for thyroid hormones	**T_4**: upper reference range for age Example: **Free T_4**: reference range: 0.8-2.3 ng/dL, aim for 1.4-2.3 ng/dL **Total T_4**: 10-16 µg/dL in the firsts 2 years of life;thereafter, upper half of the age-specific reference range **TSH**: < 5 µU/mL, optimally 0.5-2.0 µU/mL

Modified from LaFranchi, 2011 (43).

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