

AVANCES EN TIROIDES

Pathogenesis of Transient Congenital Hypothyroidism

Patogenia del hipotiroidismo congénito transitorio

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Abstract

Transient congenital hypothyroidism (TCH) refers to congenital hypothyroidism which spontaneously resolves in the first few months or years of life. This can be challenging to predict using available markers, and diagnosis usually requires withdrawal of levothyroxine therapy at around three years of age. TCH is a major contributor to primary congenital hypothyroidism and its incidence has increased in recent studies. Causes include genetic factors, especially *DUOX2* and *DUOX2* mutations, as well as exposure to maternal antibodies, specific medications and iodine deficiency or excess. The relative contributions and interactions of intrinsic and extrinsic factors and the extent to which TCH may be prevented or recur require evaluation in future population-based studies.

Introduction

Primary congenital hypothyroidism (CH) is the most common neonatal endocrine disorder, affecting approximately 1 in 2,000 babies depending on the specific population and the neonatal screening protocol. Most CH (approximately 65%) occurs due to thyroid dysgenesis, usually characterized by thyroid ectopy (ectopic thyroid development) or athyreosis (complete absence of the thyroid gland) and, less frequently by thyroid hypoplasia. The remaining cases have a normally-located gland *in situ*, sometimes with associated goitre, in which thyroid hormone

biosynthesis is inadequate (GIS CH). Untreated CH results in profound, irreversible neurodevelopmental delay, and developed countries therefore offer neonatal screening to facilitate early detection and treatment. The strategy for this is variable, but in most countries screening is TSH-based, with TSH results above a certain threshold triggering formal evaluation of thyroid function. Postnatally, a TSH surge and an associated peak in T4 concentrations occurs within minutes to hours of birth, returning to baseline in the first days of life. The TSH thresholds defining a positive neonatal screening result aim to minimize false-positive referrals due to the physiological TSH surge, whilst avoiding false negatives resulting in failure to diagnose 'true' CH^(1,2).

Most children with primary CH develop permanent thyroid dysfunction. However, in a sizeable number of affected children, thyroid function recovers in early childhood, permitting withdrawal of levothyroxine treatment by the age of three years. These children, who usually have GIS CH, are said to have transient CH (TCH). Another category of infants exhibit transient neonatal hyperthyrotropinaemia, with elevated neonatal TSH and normal FT4 concentrations which normalize over time. This entity is poorly understood and may represent a delay in the resolution of the postnatal TSH surge or a persistence of relative fetal pituitary insensitivity to thyroid hormone. In some cases, overt hypothyroidism or persistent subclinical hypothyroidism may manifest in later childhood, due to aetiological overlap with CH⁽²⁾.

Epidemiology of transient congenital hypothyroidism

The incidence of CH has increased worldwide in recent decades, with the majority of studies demonstrating a predominant increase in GIS CH, although thyroid

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ectopy increased in one study⁽³⁻⁵⁾. Increased detection is a major contributor to these findings as a result of altered screening algorithms and lower TSH diagnostic thresholds following the development of high sensitivity assays^(6,7). However, altered ethnic mixes in the screened populations, increasing preterm birth survival and potentially altered environmental contributors may also be implicated as well as hitherto unidentified factors^(4,8-10).

The majority of studies specifically including TCH also demonstrate an increase over time, such that this may now include more than one-third of children with GIS CH^(5,6,11). Although these findings may be strongly influenced by decreases in TSH screening cutpoints over time, additional factors, e.g., population iodine status, may be involved⁽¹²⁾. In some populations, the incidence of TCH is reported to be stable⁽¹³⁾.

Diagnosis of transient congenital hypothyroidism

The most recent European consensus guidelines advocate evaluation for TCH in children without a definitive diagnosis of permanent CH (e.g., those in whom thyroid morphology is compatible with hormone synthesis) and who have relatively low daily levothyroxine dosage requirements which are stable or decreasing without a compensatory rise in TSH ($\leq 25 \mu\text{g}$, consider if $<3 \mu\text{g}/\text{kg}/\text{day}$). Clinicians are advised to wean levothyroxine over four to six weeks, and then to reevaluate thyroid function four weeks after treatment cessation. If the patient remains biochemically euthyroid according to an age-appropriate reference range, it is likely that the thyroid has recovered. In order to allow for a period of mild TSH elevation during hypothalamic-pituitary-thyroid axis recovery, repeat thyroid function tests are recommended after four weeks of treatment if TSH is above the upper limit of normal, but less than $10 \text{ mU}/\text{L}$ ⁽¹⁴⁾.

Predictors of transient congenital hypothyroidism

A plethora of studies have sought to use clinical and biochemical data to predict the likelihood of transient CH. This would facilitate targeted levothyroxine withdrawal in individuals most likely to exhibit recovery of thyroid function. However, accurate predictors have proved elusive. The most robust indicator of TCH seems to be lower levothyroxine requirements throughout the course of treatment. Most studies have also shown lower TSH levels at diagnosis in comparison to those seen in permanent CH, and an absence of TSH elevation during treatment⁽¹⁵⁻¹⁷⁾. Additional predisposing factors include low birth weight, male sex, non-White ethnicity, prematurity and neonatal intensive care admission and maternal thyroid disease, but associations may be variable^(14,15,18,19). Given the difficulties in predicting TCH, all children with GIS CH should be reassessed before the end of the

third year of life to determine whether a trial without levothyroxine treatment is warranted⁽¹⁴⁾.

Pathophysiology of transient congenital hypothyroidism

TCH occurs due to a compromised thyroid, which subsequently recovers in early childhood. Both endogenous and extrinsic factors influencing thyroid hormone biosynthesis, have been implicated in the pathophysiology of TCH. Extrinsic causes such as medication may affect the neonate alone, or maternal factors may transfer to the fetus or neonate transplacentally or through breastmilk. Maternally-derived causes include antibodies which may cross the placenta from the mother to fetus, medication, and maternal iodine status. Extrinsic factors generally permit thyroid recovery when they are withdrawn, resulting in TCH. Intrinsic causes include genetic mutations causing mild dysmorphogenesis (Fig. 1).

The magnitude of thyroid dysfunction will be indirectly proportional to the efficiency of thyroid hormone biosynthesis, and will depend both on the degree of thyroid functional impairment, and the demands for hormone synthesis. Thyroid hormone biosynthesis is at its peak in the neonatal period but decreases rapidly during the first year of life. Further transient increases in thyroid hormone biosynthesis requirements are observed during puberty and throughout pregnancy (in females). A thyroid gland with an intrinsic defect resulting in partially impaired thyroid hormone biosynthesis may be able to maintain euthyroidism at times when thyroid hormone requirements are at basal levels, especially if there are compensatory pathways, e.g., *DUOX1* in the context of *DUOX2* mutations. As a result, although levothyroxine supplementation may be required during the neonatal period when there is increased metabolic demand, it can be withdrawn when thyroid hormone biosynthesis declines in early childhood (Fig. 2).

Exogenous causes

Antibody-mediated transient congenital hypothyroidism (Maternal Graves disease)

Maternal Graves disease may be associated with blocking anti-TSHR antibodies which cross the placenta and may inhibit the fetal TSHR from mid-gestation onwards, leading to potentially profound neonatal hypothyroidism⁽²⁰⁾. Despite elevated thyroglobulin (if measured) and ultrasonographic evidence of a thyroid gland *in situ*, thyroidal technetium uptake may be reduced (probably due to impaired NIS expression) leading to apparent athyreosis. The antibodies usually clear the circulation after three to six months, following which hypothyroidism will resolve unless potent blocking antibodies have caused impaired thyroid development and permanent CH⁽²¹⁾.

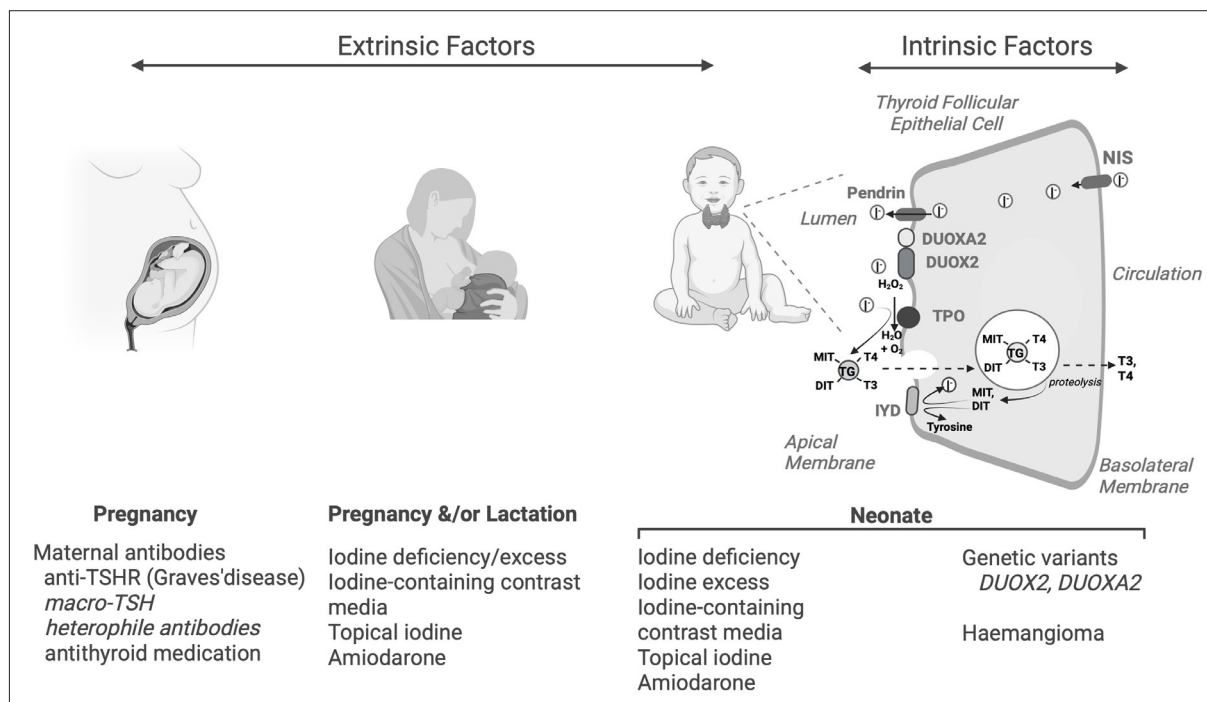


Figure 1. Schematic to show intrinsic and extrinsic causes of TCH. Extrinsic causes may be transmitted from the mother to fetus transplacentally or to the neonate in breast milk, as well as directly affecting the neonate. Intrinsic causes principally comprise genetic mutations in the NADPH-oxidase DUOX2 and its accessory protein, DUOXA2, which produce H₂O₂ required for the oxidation of iodide during the process of thyroid hormone biosynthesis. The key molecules involved in this process are summarized in the schematic of the thyroid follicular cell. NIS: sodium iodide symporter, MIT, DIT: mono- and diiodotyrosine, TPO: Thyroid peroxidase, IYD: iodotyrosine dehalogenase 1. Created with Biorender.com.

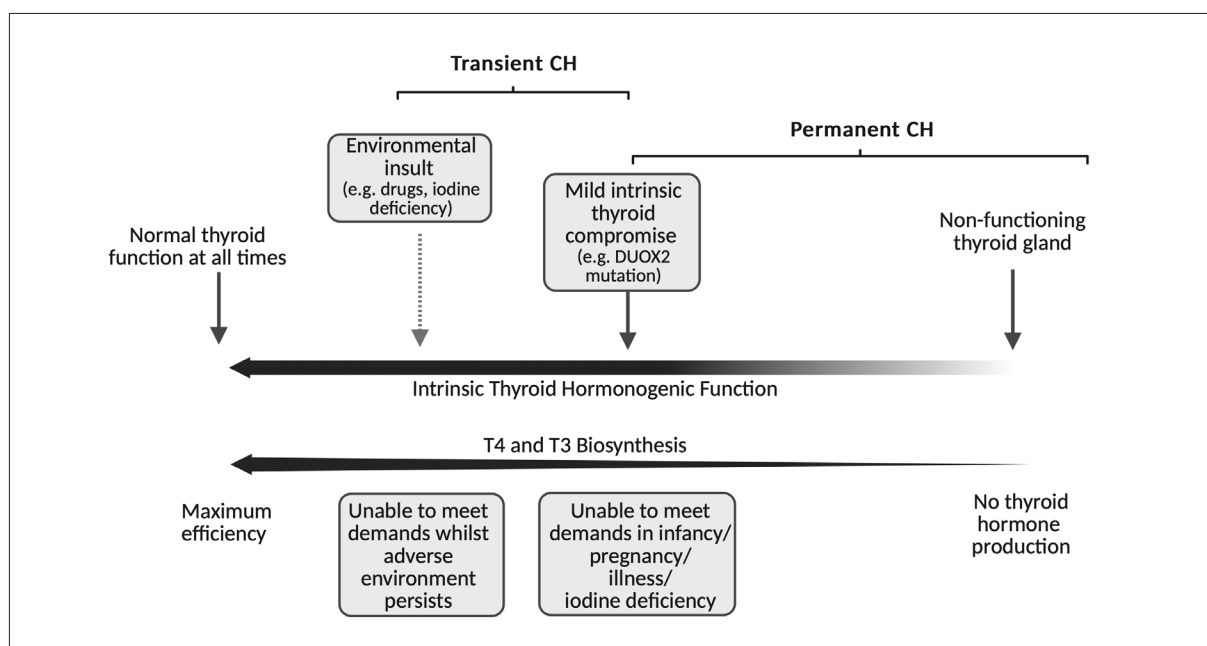


Figure 2. Schematic to show the association between efficiency of thyroid hormone biosynthesis and transient CH. Created with Biorender.com.

Spurious congenital hypothyroidism due to antibody interference

Artefactual TCH may occur due to the transplacental passage of maternal antibodies which interfere with the TSH assay, causing spuriously high TSH results,

resulting in an incorrect diagnosis of CH, despite normal FT₄ and FT₃ levels (often disproportionately so for the degree of TSH elevation). Either anti-animal or heterophile (polyspecific) antibodies targeting assay reagents or anti-TSH antibodies resulting in the formation of bioinactive macro-TSH complexes may

cause spurious TSH elevation. Interfering antibodies may have variable effects in different assays, resulting in inter-assay variability in TSH measurement, and since the antibodies originate in the mother, maternal TSH is also elevated⁽²²⁾. The prevalence of macro-TSH is estimated at around 0.79% in patients with subclinical hypothyroidism, and may result in inappropriate levothyroxine treatment in both mother and baby⁽²³⁾. The diagnosis can be made following polyethylene glycol (PEG) precipitation to remove high molecular weight proteins which results in low recovery of TSH. The presence of macro-TSH can be confirmed using gel filtration chromatography to demonstrate a high molecular weight TSH peak fraction that approximates the molecular size of IgG. Neonatal TSH assay interference resolves at around 8 months of age when maternal IgG is cleared, whereas the TSH level of the mother remains high⁽²⁾.

Medication

Maternal antithyroid drugs

Maternal hyperthyroidism frequently requires treatment with thionamide medication during pregnancy to permit tight endocrine control and to reduce the risk of adverse outcomes. Propylthiouracil (PTU) is most commonly used in early pregnancy as it carries the lowest risk of teratogenicity, but methimazole or carbimazole may be used from the second trimester onwards. Both have similar kinetics of placental transfer, and may cause fetal hypothyroidism or neonatal transient CH, especially at higher doses, even when maternal thyroid hormone levels are normal. Both methimazole and PTU are rapidly cleared from the fetal circulation; neonatal-transient hypothyroidism due to ATDs therefore usually resolves within a few days of birth^(24,25).

Amiodarone

Amiodarone is a commonly used anti-arrhythmic agent which may be prescribed for cardiac dysrhythmias in both mother and neonate. It contains a high iodine load and may provoke hypothyroidism due to the Wolff-Chaikoff effect, either directly or by transplacental passage, thereby resulting in transient CH, which may be profound and associated with goitre, especially after transplacental exposure⁽²⁶⁾.

Iodine

Iodine deficiency

Iodine is an essential trace mineral required as a substrate for thyroid hormone biosynthesis. However, both iodine deficiency and excess may cause TCH. At the most severe end of the spectrum, profound iodine deficiency *in utero* causes endemic cretinism. Although this is rare in developed countries, milder

degrees of iodine deficiency are re-emerging. Maternal iodine deficiency may result in compromised fetal or neonatal thyroid function with compensatory neonatal TSH elevation, thyroglobulin elevation and increased thyroid volume, depending on the severity of the deficit. The neonatal thyroid is exquisitely sensitive to iodine deficiency due to its low thyroidal iodine content and accelerated iodine turnover compared with adults. However, CH may correct itself once neonatal iodine intake increases⁽²⁷⁾.

In keeping with a causal link with TCH, the prevalence of TCH has been found to be higher in areas where iodine deficiency is common, e.g. eight times more common in Europe compared to North America in one study, and in iodine-deficient areas in Algeria compared with iodine-replete regions (incidence 0.22% vs 0.09%)^(27,28). A more recent systematic review and meta-analysis investigating the association of neonatal TSH with maternal iodine status during pregnancy and the early postpartum period found that TSH levels in cord samples of neonates born to mothers with iodine deficiency were significantly higher than those born following iodine-sufficient pregnancies⁽²⁹⁾.

Iodine supplementation has been shown to prevent TCH, e.g. in Belgian preterm infants supplemented with 30 µg potassium iodide/day and following iodine supplementation programmes. Maternal iodine supplementation before or during pregnancy may also prevent the severe hypothyroidism associated with iodine deficiency and thiocyanate overload in Zaire⁽²⁷⁾.

Iodine insufficiency has been noted in several population surveys, including those evaluating pregnant women⁽³⁰⁻³³⁾. Although the association between declining iodine status and TCH has not been evaluated in detail, and may not be implicated in some cohorts, iodine deficiency remains a strong contender for mediating some of the observed increase in TCH⁽²⁾.

Iodine excess

Excess iodine can also result in impaired thyroid hormone biosynthesis due to the Wolff-Chaikoff effect. Although a normally functioning thyroid gland downregulates the sodium-iodide symporter (NIS) and 'escapes' from the Wolff-Chaikoff effect after around two weeks, the fetal thyroid gland does not have an adequate escape mechanism until around 36 weeks gestation. Fetal and neonatal thyroid (especially in preterm infants) is therefore highly susceptible to iodine excess from 18 to 20 weeks, when fetal thyroidal iodide uptake begins⁽²⁾. Iodine exposure may cause TCH through transient topical use of iodine-containing disinfection agents in the peri- and neonatal periods, which is now not recommended due to the risk of thyroid compromise⁽¹⁴⁾. Maternal iodine

overconsumption through food products containing seaweed or iodine supplements, (inadvertently including in herbal remedies) has anecdotally been associated with neonatal transient or mild persistent CH. Neonatal renal iodine clearance is low, and iodine excess may therefore result in blockade of thyroidal iodine transport for weeks to months^(34,35). Neonatal administration of iodine containing contrast medium (ICM) may also cause hypothyroidism, especially in premature neonates (up to 18% in a systematic review)^(36,37). This is particularly relevant in neonates with congenital heart disease, who may have multiple exposures to ICM as part of investigation and management.

Genetic causes of transient congenital hypothyroidism

Thyroid hormone biosynthesis requires a complex pathway of transporter molecules and enzymes. Thyroidal iodide uptake is mediated by the sodium-iodide symporter (NIS), and iodide efflux into the follicular lumen is mediated by transporters including pendrin. Iodide is then oxidized and incorporated into tyrosyl residues on the surface of thyroglobulin to form mono- and di-iodotyrosyl (MIT and DIT) with coupling of MIT and DIT catalyzed by the thyroid peroxidase enzyme (TPO), resulting in formation of thyroid hormones (Fig 1). The NADPH-oxidase DUOX2 and its accessory protein DUOXA2 synthesize the H₂O₂ essential for iodide oxidation. Both monoallelic and biallelic DUOX2 and DUOXA2 mutations have been reported in association with congenital hypothyroidism. Intriguingly, the relatively high (>1%) population frequency of loss-of-function variants in these genes supports the notion that heterozygous mutations require the contribution of other modifiers in order to cause CH. More than 50% of individuals with CH associated with DUOX2 or DUOXA2 mutations have been reported as exhibiting TCH, including those harbouring biallelic truncating DUOX2 mutations. Mutations in other genes in the thyroid hormone biosynthesis pathway may also cause congenital hypothyroidism, but this tends to be permanent, although in some cases the biochemical defect may be mild and variable with time. However, it is important to note that an intrinsically defective thyroid may decompensate again in later life in the presence of stressors, and recent studies suggest that hypothyroidism may recur in individuals with DUOX2 mutations who have been weaned off levothyroxine⁽³⁸⁻⁴⁰⁾.

Conclusion

The incidence of TCH is increasing, and further studies are required to understand the contributions of both well-defined and hitherto unidentified genetic and environmental determinants. Although TCH is usually associated with a normally located thyroid

gland *in situ* and low levothyroxine requirements, it cannot be predicted accurately on the basis of clinical or genetic findings, and requires a supervised trial of levothyroxine therapy for diagnosis. The long-term recurrence risk for TCH is unknown and long-term monitoring for recurrent thyroid dysfunction should be offered in confirmed, genetically-mediated cases with intrinsic thyroid compromise, particularly at times of increased demand, such as during pregnancy.

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