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# Congenital Hypothyroidism

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Sanjay Saran

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## Abstract

Congenital hypothyroidism is one of the commonest preventable causes of mental retardation is also the most common congenital endocrine disorder of childhood. The subtlety of clinical features and protective effect of the maternal hormone on fetal brain after crossing the placenta mask the clinical features. The incidence varies from 1 in 4000 to 1 in 1000 in newborn infants in various parts of world and is increasing world-wide. Thyroid agenesis remains the most common etiology of CH and other causes are dysmorphogenesis, defects in peripheral thyroid hormone transport, metabolism, or action. CH is usually diagnosed after neonatal screening tests and if treatment started within in few weeks of birth neurodevelopmental outcome is usually normal. Levothyroxine (T4) remains the treatment of choice as most brain T3 is derived from local monodeiodination of T4 and studies have shown normal serum level of T3 in infant treated with T4 alone.

**Keywords:** congenital, hypothyroidism, levothyroxine, TSH, thyroid

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## 1. Introduction

Congenital hypothyroidism (CH), one of the commonest preventable causes of mental retardation is also the most common congenital endocrine disorder of childhood [1]. Neurodevelopmental outcome is usually better if treatment is started within in few weeks of birth [2]. The subtlety of clinical features and the maternal hormone crossing the placenta provides a protective effect on the fetal brain masking the clinical signs [3]. In addition to this even the most severe forms of CH have some functioning residual thyroid tissue further making clinical diagnosis difficult [4]. As the age of the neonate progresses so does the hypothyroxinemia leading to progression of the clinical signs and symptoms which increases the risk for irreversible brain injury. To prevent this, treatment needs to be started as soon as possible after

birth. For all the above reasons, screening has evolved as the best way to detect infants with CH in developed countries. In North America, more than 1400 infants out of the 5 million newborns screened are diagnosed with CH annually.

## 2. Epidemiology

The incidence of CH varies from 1 in 4000 to 1 in 1000 in newborn infants as has been reported from various parts of world [5]. Developing countries like India and Iran have a higher incidence of CH [6, 7]. In countries like The US, Canada, New Zealand, Italy, Greece and Argentina the incidence of CH has nearly doubled since the introduction of newborn screening programmes [5, 8–12]. Widespread lowering of screening cutoffs in newborn screening programs [5, 8], increase detection of milder cases of CH, increase screening of higher risk newborn preterm and low birth infants, increased number of birth among Hispanic and of low birth weight [13] are some of the supposed causes that have been proposed as a possible cause for the increase in the incidence of CH. The incidence of CH is higher among Hispanic and Asian individuals and lower in black individuals [10, 13]. There has been a dramatic increase in the incidence of congenital hypothyroidism detected by the newborn screening programs, the incidence has risen from 1:3985 (in 1987) to 1:2273 (in 2002) [14]. This dramatic increase may be attributed to a spurt in the Asian (37%) and Hispanic (53%) births over the same period [13].

## 3. Etiology

Abnormal development of thyroid gland (thyroid dysgenesis) is the most common cause of CH. Thyroid dysgenesis accounts for 85% of cases of CH and is usually sporadic. It has three major forms thyroid ectopy, athyreosis and thyroid hypoplasia. Thyroid ectopy: it is the most common form and accounts for two thirds of cases of thyroid dysgenesis and is twice more common in females [15]. The exact etiology of thyroid dysgenesis is not known but largely its considered a sporadic disease and although the etiology remains elusive in most of cases some mutations in transcription factor genes i.e. TSHR, PAX8, NKX2-1, FOXE1, that regulate thyroid gland development have been reported, but only 2–5% of cases with thyroid dysgenesis are found to have such genetic mutations [16]. Recently, several other genes have found to be associated with thyroid gland dysgenesis, including NKX2-5, JAG1 and GLIS3 although each of them contributes to only a small fraction of cases [17–21]. Each of these transcription factors has a role in the development of organ systems too, and mutations of these genes are generally associated with additional congenital defects. In remaining one-third of cases, CH results from absence of thyroid (athyrosis) and thyroid hypoplasia. Dyshormonogenesis, or defects in peripheral thyroid hormone transport, metabolism, or action are accounted in approximately 15% of cases [22]. Defects in thyroid hormone biosynthesis are familial and usually autosomal recessive in inheritance [23]. These include mutations in the genes coding for the sodium-iodide symporter (NIS; SLC5A5), thyroid peroxidase (TPO), thyroglobulin (Tg), apical iodide transporter pendrin (PDS; SLC26A4), iodotyrosine deiodinase (IYD), dual oxidase (DUOX2) and its necessary protein(DUOXA2) [23]. Defective thyroid hormone

transport (mutations in monocarboxylase transporter 8), metabolism (selenocysteine insertion sequence-binding protein 2), or resistance to action (mutations of thyroid hormone receptor) are some rare causes. Among the aforementioned defects, mutations of the thyroid peroxidase (TPO) gene form the most prevalent cause of inherited defects in CH [24]. The incidence of thyroid dysmorphogenesis has been increasing and now accounts for 30–40% case of CH but thyroid dysgenesis remains the most common cause of CH [12].

Maternal thyrotropin receptor–blocking antibodies, exposure to maternal antithyroid medications, iodine deficiency or iodine excess are the major causes of transient CH in children.

Central congenital hypothyroidism is rare and is usually associated with and is usually associated with developmental anomaly of the pituitary gland and is usually associated with other pituitary hormone deficiencies like adrenocorticotropin and gonadotropins [25]. If isolated, it usually results from a mutation in the thyroid stimulating hormone  $\beta$  TSH $\beta$  subunit gene or TRH receptor gene. Less often it is due to mutation in transcription factor gene regulating pituitary development i.e. HESX1, LHX3, LHX4, OTX2, SOX3, PIT1 and PROP1 [1].

## 4. Diagnostic evaluation

In countries with newborn screening programs CH is diagnosed after neonatal screening tests. However, only 25% of the world wide birth population has the access and undergoes the said screening tests [26]. For the remaining 75% infants, particularly concentrated in developing countries, clinical suspicion of hypothyroid leads to thyroid function evaluation.

### 4.1. Newborn thyroid screening protocols

48–72 h after birth is the ideal time for the newborn screening tests, the reason being that the physiological surge in TSH that occurs after the first hours after birth to a peak serum level of 80 mIU/L slowly starts to decrease over the next several days [27]. Sample taken within 48 h of birth may lead to false positive results whereas screening done in very sick newborn or following blood transfusion may lead to false negative result.

In case of a critically ill new born, preterm birth or in case of a home delivery sample should be collected by 7 days of age. Capillary blood samples taken by heel prick method are placed on circles of specialize filter paper, dried at room temperature, then sent to a centralized laboratory. Second blood sample taken at 2–4 week is a part of the protocol in some screening programs. The additional incidence of CH based on a second screening at 2 weeks of age is approximately 1 in 30,000 [28, 29]. Preterm and LBW infants, critically ill infants, same-sex twins, and infants whose initial screen was performed in the first 24 h of life are some examples where a routine second screening must be performed [30].

Earlier the screening protocol for CH was T4 estimation followed by TSH only if t4 was low however with increasing accuracy of TSH assays on small volumes of blood, initial TSH testing has become the sine qua non of most screening protocols [31]. Both methods allow for the detection of most of the infants having CH but each method has its own merits and demerits. Measuring T4 first and then TSH detects some cases of secondary hypothyroidism and

infants that might have “delayed TSH elevation” whereas measuring TSH first and then T4 also detects mild or subclinical forms of hypothyroidism. Broadly speaking, if the screening T4 value is less than 10th percentile of cut off and/or the TSH is greater than 40 mU/L, the infant should be called again for confirmatory serum testing. In cases having “intermediate results,” TSH 20–40 mU/L, recommendation is to repeat TSH screening in early second week of life. A TSH value <20 mIU/L is considered as normal.

#### **4.2. Confirmatory serum thyroid testing**

Diagnosis must not be completely and solely reliant on the screening tests only they must be confirmed by serum testing, venipuncture blood should be drawn and serum should be sent for TSH and free T4, or total T4 and T3 resin uptake as some measure of binding proteins. These serum based results must be compared with age normalized values as during the first week of life TSH and T4 are fluctuant [32]. Most confirmatory serum tests could be obtained in first 2 weeks of life, as during this upper TSH range has fallen to an around 10 mU/L. Although all hormones are higher during first week of age they come down to infancy range within 2–4 weeks.

### **5. Test results**

#### **5.1. Low T4 and elevated TSH values**

A low total serum T4 or free T4 level along with an elevated serum TSH level confirms the diagnosis of primary hypothyroidism and levothyroxine (L-T4) must be started immediately after the confirmatory tests are done even before the results are available. Before age of 2 weeks, venous TSH >20 mIU/L and after 2 weeks, TSH > 10 mIU/L, suggests primary CH [33]. Serum T4 < 10 µg/dL (<128 nmol/L) or FT4 < 1.17 ng/dL (<15 pmol/L) is considered low in infancy.

#### **5.2. Normal T4 and elevated TSH values**

A transient or permanent thyroid dysfunction or delayed maturation of the hypothalamic–pituitary axis is indicated by normal levels of total T4 or free T4 along with elevated TSH. Initiating levothyroxine in such cases is still controversial. Since TSH concentration is the most sensitive indicator of hypothalamic-pituitary-thyroid axis therefore when confirmatory serum TSH level is between 6 and 20 mIU/L with normal FT4 levels, it is reasonable to watch serum thyroid function tests closely (every 1–2 weeks) and not start LT4 and if TSH is increases or if FT4 decreases to below normal level, treatment should be initiated. After 2 weeks of age a TSH > 10 mU/L is considered abnormal [34, 35]. And if TSH elevation persists, the infant must be treated.

#### **5.3. Low T4 and normal TSH values**

Hypothalamic immaturity particularly in preterm infants, in infants during illness, in central hypothyroidism or in primary hypothyroidism and delayed TSH elevation low T4 with normal TSH may be seen. No guidelines exists for the follow-up of these patients, but they

can be followed with serial filter-paper screening tests until the T4 value becomes normal, or a second blood sample for measurement of serum FT4 and TSH can be obtained. Such infants are usually found to have normal thyroid profile on subsequent screening tests. Their treatment (except those with central hypothyroidism) with L-T4 has not yet been shown to be beneficial [36].

## **6. Diagnostic studies to determine an underlying etiology**

Since additional investigations for etiology do not alter the treatment plan they can be delayed. Treatment of CH should never be deferred after confirmation pending the determination of etiology.

### **6.1. Thyroid radionuclide uptake and scan**

Thyroid radionuclide uptake and scanning is the most accurate imaging modality to determine the size and location of thyroid tissue. Iodine-123 (I-123) or sodium pertechnetate 99 m (Tc99m) are tracers of choice as I-131 delivers a higher dose of radioactivity. Radionuclide uptake and scan is used to identify thyroid aplasia (absent uptake), hypoplasia (decreased uptake, small gland in a eutopic location) or an ectopic gland. Other conditions not showing any uptake include; TSH $\beta$  gene mutations, TSH receptor inactivating mutations, iodide trapping defects and in those with maternal thyrotropin receptor blocking antibodies (TRB-Ab). Dyshormonogenesis beyond trapping of iodide results in a large gland in a eutopic location with increased uptake on the scan. A perchlorate discharge test can be performed to confirm the diagnosis of dyshormonogenic CH.

### **6.2. Thyroid ultrasound**

When it comes to etiology determination thyroid ultrasound is usually the first modality performed. It confirms thyroid aplasia when radionuclide scan show absent uptake. TSH $\beta$  gene mutations, TSH receptor inactivating, iodide trapping defect and maternal TRB-Ab shows the absence of radionuclide uptake in the presence of thyroid gland in the normal position. Dyshormonogenesis is associated with absent uptake in radionuclide scan and large thyroid in ultrasound. Color Doppler flow may be able to detect up to 90% of cases of ectopic thyroid [37].

### **6.3. Serum thyroglobulin (Tg) measurement**

Serum thyroglobulin is reflective of the thyroid mass and is usually raised in increased activity of the thyroid gland. In a recent study, Beltrão et al., suggested that color Doppler ultrasound combined with serum thyroglobulin measurement may become very valuable tools for the diagnosis of the cause of CH and will also help minimize more harmful tests, like radionuclide scan [38]. Increased thyroglobulin levels and absent uptake on radionuclide scan suggests presence of thyroid gland along with a TSH receptor inactivating mutation, a trapping defect, or maternal TRB-Ab, rather than aplasia.



#### 6.4. Thyroid receptor antibody

Transient CH in children can also be caused by maternal thyroid receptor blocking antibodies TRB-Ab. Absent radionuclide uptake with small or normal sized eutopic gland suggests transient congenital hypothyroidism as a result of transplacental passage of the antibody from the mother to the child. For confirmation the measurement of serum TRB-Ab in mother and/or infant may be done by a thyrotropin-binding inhibitor immunoglobulin (TBII) assay.

#### 6.5. Urinary iodine estimation

24 h urinary iodine excretion approximates the iodine ingestion. For neonates the normal range is approximately 50–100 mg/24 h. Urinary iodine measurement may provide confirmation regarding iodine deficiency or excess.

### 7. Management

CH remains the most common preventable cause of mental retardation. Studies have shown that timing and dosing of thyroid hormone replacement are both crucial for neurological outcome. The infant must be rendered euthyroid as early as possible by starting the treatment promptly and at sufficient dose, as there is an inverse relationship between intelligence quotient (IQ) and the age of diagnosis. Despite early diagnosis the neurological outcome may be poor due to delay in starting treatment, lower starting thyroid hormone dosing and severity of the hypothyroidism, which itself correlates with the underlying etiology [39].

#### 7.1. Formulation

Levothyroxine (L-thyroxine) remain the treatment of choice. Although biologically active form is triiodothyronine (T3) but most brain T3 is derived from local monodeiodination of T4. As studies have shown normal serum level of T3 in infant treated with T4 alone, so treatment with T3 is not essential for normal neurological outcome/brain development [40]. Currently, only tablets form of L-thyroxine are approved for use owing to inconsistent delivery of liquid formulations. However, in some countries in Europe, L-thyroxine suspension is also available and is used to normalize thyroid function.

#### 7.2. Administration

Crushed levothyroxine (L-thyroxine) tablet is mixed with 1–2 ml of breast milk, formula or water and resultant suspension is squirted into cheek pad or put on open nipple for infant to feed. Various substances like such as calcium and iron preparation, soy protein formula, sucralose, aluminum hydroxide and cholestyramine interfere levothyroxine (L-thyroxine) absorption through gut and thus should not be given together [41, 42]. Although, recommendation is to take levothyroxine (L-thyroxine) empty stomach but for infant it may not be feasible.

### 7.3. Dosages

For the optimal neurodevelopmental outcome, the treatment goal is to normalize T4 and TSH within 2 and 4 weeks respectively [33, 43, 44]. In a study infants had significant lower cognitive, attention and achievement scores who took more than 2 weeks to normalize thyroid function compared to infants who attained normal thyroid function at 1 or 2 weeks of treatment [45]. Adequacy and the timing of treatment determines optimal neurodevelopmental outcome and thus American academy of pediatrics and European society of pediatric endocrinology recommend 10–15 µgm/kg/day as initial dose [46]. Studies show that this dose normalizes serum T4 within 3 days and TSH within 2–4 weeks. To achieve these goals, it is important to start higher initial dose of the recommended range in case of severe CH. In a study infants who were started on higher initial doses of 50 µgm had full-scale IQ scores 11 points higher than those started on lower initial doses of 37.5 µgm [45].

### 7.4. Target concentrations

The target T4 concentrations lies in the upper half of reference range according to the Guidelines issued by the American academy of pediatrics and European society for pediatric endocrinology [30, 47–49]. Target values for T4 being 10–16 µgm/dl; FT4 1.4–2.3 ng/dl and TSH <5 µU/dl (optimally 0.5–2.0 µU/dl) for initial 3 years of life following this T4 should be kept in the upper half of normal range. Low IQ in infants with T4 concentration below 10 µgm/dl and TSH above 15 µU/dl was seen during the first year of life compared to those had serum T4 more than 10 µgm/dl [50]. Better intellectual outcome in children with CH was seen with higher doses of levothyroxine (L-thyroxine) [51]. Contrary to this other studies have shown behavior problems like increased anxiety, social withdrawal and poor concentration with higher doses in children at age of 8 years. Thus demonstrating potential dangers of overtreatment with levothyroxine in CH children [52].

## 8. Follow-up

Congenital anomalies are also more frequent in CH than in general population (10% in CH compared to 3% in general population) most common of these anomalies is cardiac malformation particularly pulmonary stenosis, atrial septal defect and ventricular septal defect. Adequate monitoring is required to maintain the thyroid functions within the recommended levels. The American Academy of Pediatrics recommends the following monitoring schedule [53].

- At 2 and 4 weeks after the initiation of L-thyroxine treatment.
- Every 1–2 m during the first 6 m of life.
- Every 3–4 m between 6 m and 3 years of age
- Every 6–12 m thereafter until growth is complete



- Four weeks after any change in dose or more frequently if results are abnormal or non-compliance is suspected.

To ensure adequate growth and neurological development of the infant clinical evaluation should be carried out even more frequently than lab investigation.

### 8.1. Unresolved controversy

The incidence of congenital hypothyroidism is seemingly on the rise. Whether this increase is absolute or the result of lowering of screening test cutoff or changes in the racial and demographic profile or something else remains to be determined. This rise may also be the result of a larger reach of the screening test or the detection of infants with mild hypothyroidism and those with “delayed TSH rise”. As already mentioned the most common cause of CH is thyroid dysgenesis, but the underlying etiology of thyroid dysgenesis remains an enigma. Only 2% cases of thyroid dysgenesis caused by genetic mutation in genes that encode for thyroid transcription factors. The other issue at hand is whether the rise of TSH is permanent or temporary we require more studies in affected infants detected by abnormalities on a second screening test to resolve this controversy.

## 9. Conclusion

Congenital hypothyroidism (CH) is one of the most common preventable cause of mental retardation. Screening of large populations of newborns is best method to diagnose infants with CH. If the diagnosis is made and treatment started within a few weeks of birth, neuro-developmental outcome generally is normal. The underlying etiology of the most common cause of CH, thyroid dysgenesis, is largely unknown.

### Author details

Sanjay Saran

Address all correspondence to: drsanjaysaran@gmail.com

Department of Endocrinology, SMS Medical College and Associated Group of Hospitals, Jaipur, India

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