

Congenital Hypothyroidism

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Abstract

Congenital Hypothyroidism (CH) is one of the most common preventable causes of mental retardation with a worldwide incidence of 1: 3000-4000 live births. Ideally universal screening at 3-4 days of age should be done for detecting CH. Abnormal values on screening should be confirmed by a venous sample (using age appropriate cut-offs). Term as well as preterm infants with low T4 and elevated TSH should be started on L-thyroxine at a dose of 10-15µg/ kg/ day as soon as the diagnosis is made. Regular monitoring should be done to ensure that TSH is suppressed to within normal range and T4 is in the upper half of normal range. The outcome of CH depends on the time of initiation of therapy and the dose of L-thyroxine used with the best outcome in infants started on treatment before 2 weeks of age with a dose > 9.5µg/ kg/ day.

Keywords: congenital hypothyroidism, L-thyroxine, newborn

Congenital Hypothyroidism (CH) is one of the most common preventable causes of mental retardation. The worldwide incidence is 1:3000-4000 live births and the estimated incidence in India is 1:2500-2800 live births.¹ Thyroid dysgenesis is the commonest cause accounting for 75-80% of all cases of CH.

Embryology and physiology of the thyroid in the fetus - The thyroid gland originates as a proliferation of endodermal epithelial cells at 3 to 4 weeks of gestation. Synthesis and secretion of thyroxine (T4) and triiodothyronine (T3) starts from 12 weeks of gestation. Hypothalamic-pituitary-thyroid (HPT) axis begins to develop in the first trimester and thyrotropin-releasing hormone (TRH) and thyroid stimulating hormone (TSH) are also detectable by the end of first trimester. However, the activity of HPT axis is low with insufficient production of thyroid hormones by the fetus until about 18-20 weeks of gestation. In the second half of gestation, the T4 and TSH levels increase progressively. In the first trimester, the fetus is dependent on transplacental passage of thyroid hormones.

In the hypothyroid fetus, this transplacental passage of maternal thyroid hormones is critical for neuroprotection throughout the intra-uterine life. The cord blood T4 concentration at birth in infants who are unable to synthesize T4 is 20-30% of normal. In addition, there is increased conversion of T4 to T3 in the fetal brain by the activity of type 2 deiodinase, resulting in increased local availability of the physiologically more important T3. Near normal cognitive outcome is possible in even the most severely affected infants with CH as long as postnatal therapy is initiated early in optimum doses and maternal thyroid function is normal. In contrast, when both maternal and fetal hypothyroidism are present as in severe iodine deficiency, there is a significant impairment in neuro-intellectual development despite adequate therapy soon after birth.² Similarly, maternal subtle or overt hypothyroidism during pregnancy have also been seen to have an adverse impact on the neuro-intellectual outcome of the offspring.³

Neonatal physiology - After birth, the term baby experiences a surge of TSH as a physiological response to cold environment. The TSH concentration rises to 60-80 mU/L within 30 to 60 minutes after delivery and falls quickly in the first 24 hours to about 20 mU/L, followed by a slower decrease to below 10 mU/L after the first postnatal week. The rise in TSH initiates increase of T4 and free T4 to peak levels of 17 µg/dL and 3.5 ng/dL, respectively at 24 to 36 hours after birth with a slow decline to adult values over 4-5 weeks. Preterm infants demonstrate a similar but blunted response due to HPT axis immaturity.

Etiology of CH

CH can be permanent or transient. *Thyroid dysgenesis* is the commonest cause of permanent CH affecting 1 in 4000 live births. It is usually sporadic with a 2:1 female to male preponderance. Some of the *genes proposed as operative in dysgenesis have been recently identified as TITF1, TITF2, PAX8 and TSHR.*⁴

(Table I)

Thyroid hormone synthetic defects account for 10-15% of all cases. These are inherited as autosomal recessive disorders. The defect can lie in iodide trapping or organification, iodotyrosine coupling or deiodination and thyroglobulin synthesis or secretion. The commonest of these is a defect in the thyroid peroxidase (TPO) activity leading to impaired oxidation and organification of iodide to iodine. These disorders usually result in goitrous hypothyroidism. *Iodine deficiency* is responsible for endemic cretinism and hypothyroidism in some regions of India.

Hypothalamic-pituitary hypothyroidism has an estimated incidence of 1 in 50,000. It may be isolated or associated with deficiency of other pituitary hormones and present with hypoglycemia and microphallus. Transient hypothyroidism due to *transplacental transfer of TSH binding inhibitory immunoglobulins (TBII)* from mothers with autoimmune thyroid disease is seen

in 1: 50,000 births. Their effect wanes off by 3-6 months in the majority but may last up to 9 months. *Exposure to iodine* in sick preterm infants (e.g. application of povidone iodine for skin disinfection (Wolff-Chaikoff effect) or intake of iodine containing expectorants by pregnant mothers can also induce transient hypothyroidism.

Transient hypothyroxinemia of prematurity refers to low serum concentration of thyroid hormones in up to 85% of preterm infants in early postnatal life as compared to term infants. This reflects the underdevelopment of the HPT axis, which cannot compensate for the loss of maternal thyroid hormone in preterm infants. The normal levels of fT4 and TSH in preterm infants are presented in Table 2.⁵ There has been a concern that transient hypothyroxinemia is associated with adverse neurodevelopmental outcomes and decreased survival in affected infants.⁶

Sick euthyroid syndrome reflects suppression of the pituitary's response to TRH, with inappropriately low TSH concentrations in the context of low T3 and in the more severe cases, low T4 concentrations.

Diagnosis

Newborn screening- Ideally universal screening at 3-4 days of age should be done for detecting CH. Alternatively cord blood can also be used if screening is being done only for CH and not other inborn errors of metabolism. Universal newborn screening is currently being done in many parts of the world including Western Europe, North America, Japan, Australia, and parts of Eastern Europe, Asia, South America, and Central America. Three approaches are being used for screening:

1. Primary TSH, back up T4
2. Primary T4, back up TSH
3. Concomitant T4 and TSH

In the first approach, TSH is measured first. T4 is measured only if TSH is > 20mu/L. This approach is likely to miss central hypothyroidism, thyroid binding

globulin deficiency and hypothyroxinemia with delayed elevation of TSH. In the second approach, T4 is checked first and if low TSH is also checked. This is likely to miss milder/ subclinical cases of CH in which T4 is initially normal with elevated TSH. Concomitant measurement of T4 and TSH is the most sensitive approach but incurs a higher cost.⁷ Screening programs use either percentile based cut-offs (e.g, T4 below 10th centile or TSH above 90th centile or absolute cut-offs such as T4 < 6.5 ug/dL and TSH > 20mu/L.

Abnormal values on screening should always be confirmed by a venous sample (using age appropriate cut-offs given in Table 3⁸⁻¹⁰). Most centers initiate treatment after drawing the infants' sample if TSH > 30 mu/L or T4 is low and the decision to continue or withhold treatment is taken after obtaining the blood report. For intermediate screening values of TSH, with normal T4 (if available), the treatment is initiated only after confirmation of diagnosis based on the blood report. Among infants with proven CH, TSH is > 50 mu/L in 90% and T4 is < 6.5 ug/dL in greater than 75% of cases.

In the absence of universal screening, the newborns with the following indications should be screened:

1. Family history of CH
2. History of thyroid disease or antithyroid medicine intake in mother
3. Presence of other conditions like Down's syndrome, trisomy 18, neural tube defects, congenital heart disease, metabolic disorders, familial autoimmune disorders and Pierre- Robin syndrome which are associated with higher prevalence of CH

Thyroid function should be tested in any infant with signs/ symptoms of hypothyroidism such as postmaturity, macrosomia or wide open posterior fontanel at birth or prolonged jaundice, constipation, poor feeding, hypotonia, hoarse cry, umbilical hernia, macroglossia, or dry edematous skin in infancy.

The tests should be performed even in those infants who have a normal

newborn screening report as it is not entirely free from pitfalls. The test results should be compared to the age related norms as presented in Table 3.

Once the diagnosis is established, further investigations to determine the etiology should be done. A nuclear medicine scan using sodium pertechnetate (^{99m}Tc) is especially useful in diagnosing true athyreosis or ectopy as well as goitrous hypothyroidism due to dysmorphogenesis. However, since the scan can be done only before initiating treatment, one should not withhold therapy if it is not possible to get it performed immediately.^{11,12} A list of diagnostic studies useful in infants with congenital hypothyroidism is presented in Table 4 and an algorithmic approach to investigation in Figure 1.

When should we ask for free T4 levels?

In most situations, T4 (total) levels are sufficient for diagnosis of hypothyroidism and monitoring treatment, but free T4 can be obtained as a more robust marker of the bioavailable T4, when readily accessible. When availability or cost is a constraint, estimation of free T4 should be definitely done in the following situations:^{8, 13}:

1. In premature newborns, T4 (total) values may be low because of abnormal protein binding or low levels of thyroxine binding globulin (TBG) due to immaturity of liver function, proteinuria or undernutrition. Therefore, free T4 values provide a better estimate of true thyroid function in premature or sick newborns.
2. Free T4 should be asked for in case of finding a low T4 with normal TSH. If free T4 is normal, it can be a case of congenital partial (prevalence 1:4000-12000 newborns) or complete (prevalence 1:15000 newborns) TBG deficiency. TBG levels should be evaluated to confirm this but this test is not available routinely. If free T4 is also low along with low T4 with normal TSH, central hypothyroidism should be suspected.
3. During monitoring for adequacy of treatment, we usually monitor with T4 (total) level. This assumes a normal TBG level. This can be confirmed

by measuring free T4 or TBG levels once at the time of the first post-treatment T4 measurement.

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Treatment of CH

Term as well as preterm infants with low T4 and elevated TSH should be started on L-thyroxine as soon as the diagnosis is made. The initial dose of L-thyroxine should be 10-15µg/ kg/ day with the aim to normalize the T4 level at the earliest. Those infants with severe hypothyroidism (very low T4, very high TSH and absence of distal femoral and proximal tibial epiphyses on radiograph of knee) should be started with the highest dose of 15µg/ kg/ day.¹⁴

Monitoring of therapy:

T4 should be kept in the upper half of normal range (10-16 µg/dL) or free T4 in the 1.4 - 2.3 ng/dl range with the TSH suppressed in the normal range. T4 and TSH levels should be checked according to the following schedule:

| | |
|-------------------|----------------|
| 0-6 months: | every 6 weeks |
| 6 months-3 years: | every 3 months |
| > 3 years: | 6 monthly |

T4 and TSH should also be checked 6-8 weeks after any dosage change. Growth and development of the infant should also be regularly monitored.

It is equally important to avoid over treatment. Adverse effects of over treatment include premature fusion of cranial sutures, acceleration of skeletal maturation and problems with temperament and behavior.

Asymptomatic hyperthyrotropinemia: Elevated TSH with normal T4 values are seen commonly. This hyperthyrotropinemia can be transient or permanent. Perinatal iodine exposure is the commonest cause of transient elevation in TSH. Other causes of hyperthyrotropinemia include defects in biological activity of TSH or TSH receptor, a mild thyroid hormone biosynthesis defect, subtle developmental defects or a disturbance in the negative feedback control of TSH. Hyperthyrotropinemia in newborns is usually treated but in the presence of free T4 levels in upper half of normal range, expectant management can be followed. In case of starting treatment, a 6 week trial of

putting the child off therapy followed by measuring TSH and T4 levels should be done at 3 years of age.¹⁴

Preterm infants with low T4 and normal TSH levels (Transient hypothyroxinemia of prematurity): Use of levothyroxine in an attempt to “normalize” levels remains controversial because there is insufficient evidence that early treatment with thyroid hormone leads to improved outcomes. Larger studies, especially in the extremely preterm infants are needed to resolve this issue.¹⁵

Transient Hypothyroidism: Infants with presumed transient hypothyroidism due to maternal goitrogenic drugs need not be treated unless low T4 and elevated TSH values persist beyond 2 weeks. Therapy can be discontinued after 8-12 weeks. Intake of antithyroid drugs can be continued by the hyperthyroid mothers during breast feeding because concentration of these drugs is very low in breast milk. If we have been able to document the presence of TBII in an infant and are attributing hypothyroidism to maternal autoimmune thyroiditis, treatment should be started if T4 is low and continued for 3-6 months⁸. However, when TBII estimation is not available it is best to continue treatment till the age of 3 years and then give a trial off therapy for 6 weeks followed by retesting of T4 and TSH to determine the need for continuation of therapy. The management has been summarized in Panel 1.

Outcome: The best outcome occurs with L-thyroxine therapy started by 2 weeks of age at 9.5 µg/kg or more per day, compared with lower doses or later start of therapy. Residual defects can include impaired visuospatial processing and selective memory and sensorimotor defects. More than 80% of infants given replacement therapy before three months of age have an IQ greater than 85 but may show signs of minimal brain damage, including impairment of arithmetic ability, speech, or fine motor coordination in later life.⁷ When

treatment is started between 3-6 months, the mean IQ is 71 and when delayed

- Abnormal values on screening should always be confirmed by a venous sample using age appropriate cut-offs.
 - Investigations to determine the etiology such as scintigraphy should be done as soon as the diagnosis is made. If it is not possible, the therapy should be started without delay.
 - The initial dose of L-thyroxine should be 10-15 μ g/ kg/ day with the aim to normalize the T4 level at the earliest. T4 should be kept in the upper half of normal range (10-16 μ g/dL) with TSH level suppressed in the normal range.
 - Asymptomatic hyperthyrotropinemia should be treated unless the free T4 levels are in upper half of normal range.
 - When treatment has been started in an infant with suspected transient hypothyroidism or isolated increase in TSH or borderline values of T4 and TSH, a 6 week trial of putting the child off therapy followed by measuring TSH and T4 levels should be done at 3 years of age.
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to beyond 6 months, the mean IQ drops to 54.¹⁶

Panel 1 MANAGEMENT OF CONGENITAL HYPOTHYROIDISM

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Table 1 Etiology of CH

| | |
|----|--|
| 1. | Permanent hypothyroidism. |
| | b. Thyroid dysgenesis (aplasia, hypoplasia or ectopia) |
| | c. Thyroid hormone biosynthetic defects |
| | d. Iodine deficiency (endemic cretinism) |
| | e. Hypothalamic-pituitary hypothyroidism |
| 2. | Transient hypothyroidism. |
| | a. TSH binding inhibitory immunoglobulins |
| | b. Exposure to goitrogens (iodides or antithyroid drugs) |
| | c. Transient hypothyroxinemia of prematurity |

d. Sick euthyroid syndrome

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Table 2 Reference ranges for serum free T4 (fT4) and TSH in preterm infants

| Age in weeks | Free T4 (ng/dl) | TSH (mu/l) |
|--------------|-----------------|------------|
| 25-27 | 0.6-2.2 | 0.2-30.3 |
| 28-30 | 0.6-3.4 | 0.2-20.6 |
| 31-33 | 1.0-3.8 | 0.7-20.9 |
| 34-36 | 1.2-4.4 | 1.2-21.6 |

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Table 3 Reference ranges for T4, fT4 and TSH in term infants according to age^{8, 9, 10}

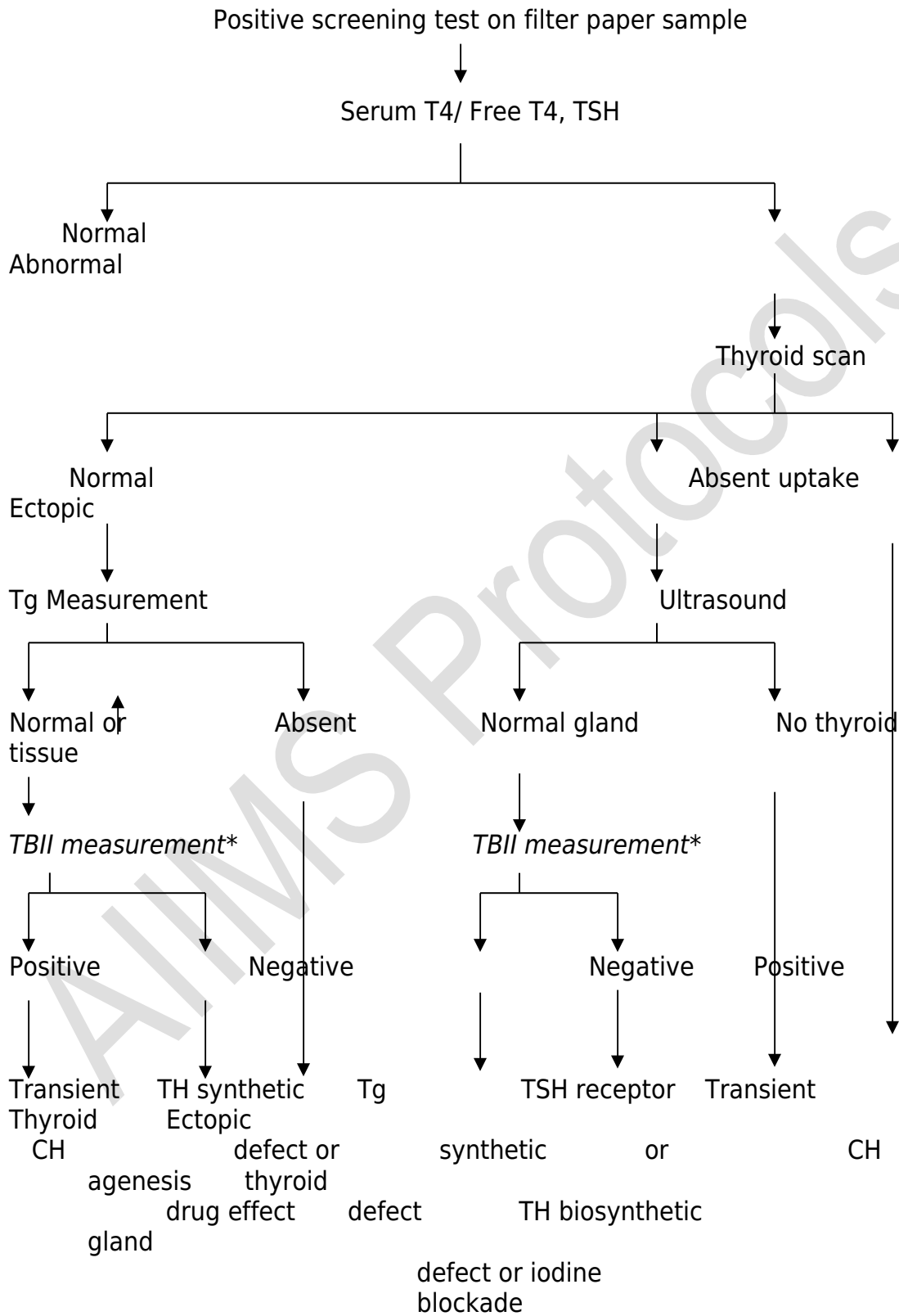
| Age | T4 (µg/dl) mean (range) | fT4 (pg/ml) mean (SD)/ range | TSH (µU/ml) mean (range) |
|----------------------|-----------------------------------|---|---------------------------------------|
| Cord blood | 10.8 (6.6-15) | 13.8 (3.5) | 10.0 (1-20) |
| 1-3 days | 16.5 (11-21.5) | * | 5.6 (1-10) |
| 4-7 days | * | 22.3 (3.9) | * |
| 1-2 weeks | 12.7 (8.2-17.2) | * | 2.3 (0.5-6.5) |
| 2-6 weeks | 6.5-16.3** | 9.0-22.0** | 1.7-9.1** |
| 6 weeks to 12 months | 11.1 (5.9-1.3) | 13.0-24.0** | 2.3(0.5-6.5) |

*No data available ** data for median/mean not available

Table 4 Diagnostic studies for evaluation of CH

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1. Imaging Studies: will determine location and size
 - a. Scintigraphy (^{99m}Tc or ^{123}I)
 - b. Sonography (less sensitive than scintigraphy)
 2. Function Studies
 - a. ^{123}I uptake
 - b. Serum thyroglobulin
 3. Suspected inborn error of T4 synthesis
 - a. ^{123}I uptake and perchlorate discharge
 4. Suspected autoimmune thyroid disease
 - a. Maternal and neonatal serum TBII measurement (not routinely available)
 5. Suspected iodine exposure or deficiency
 - a. Urinary iodine measurement
 6. Ancillary test to determine severity of fetal hypothyroidism
 - a. Radiograph of knee for skeletal maturation
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Figure 1 Approach to a newborn infant with positive screening test for CH



TBII= TSH binding inhibitory immunoglobulin (*not routinely available)

Tg= thyroglobulin, TH= thyroid hormone

Adapted from Fisher DA. Management of congenital hypothyroidism. J Clin Endocrinol Metab 1991;72:525-8.¹³

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