Thyroid Function in Children

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Introduction

Among endocrine disorders most commonly encountered in the pediatric age group, disorders of the thyroid gland are most frequent with hypothyroidism being the commonest. Goiter (thyromegaly) with or without alterations in thyroid function is not uncommon but hyperthyroidism is less frequent. The most pronounced effect of thyroid dysfunction in this age group is on growth and development but it also leads to metabolic abnormalities similar to those in adults. Thyroid hormones increase oxygen consumption, stimulate protein synthesis, affect carbohydrate, lipid and vitamin metabolism, and influence activity of other enzyme systems and growth factors. In the brain they promote cell growth, cell differentiation and induce neurotransmitter function. Their deficiency in fetal life and early infancy can lead to irreversible impairment of neurocognitive function emphasizing the crucial role of thyroid hormones on developing brain. As thyroid hormone-dependent effects on tissue maturation are age related and organ or tissue specific, the clinical consequences of thyroid dysfunction relate to age of the infant or child. Hypothyroidism after the age of three years, when most of the thyroid hormone-dependent brain development is complete, results in slow growth and delayed skeletal maturation. However, permanent effect on cognition and neurological development is not commonly reported. If hypothyroidism remains unrecognized during early childhood, physical growth potential can also be affected. Hyperthyroidism can induce rapid linear and skeletal growth and maturation; it can lead to craniosynostosis in infancy and other systemic effects which are related to increased metabolic activity due to excess of thyroid hormones. Approximately 100μg of thyroxine (T4) is secreted by the thyroid gland daily and about 90μg of iodide (15μg/kg) is the recommended daily intake during infancy and childhood with higher requirements in preterms.

Prevalence of Thyroid Disorders in Childhood in India

Siblings of index cases in India were found to have high prevalence of goiter in cases of lymphocytic thyroiditis (74%) and also in those with colloid goiter (71%). This is significantly higher than earlier reported goiter prevalence of 23% in 14,762 schoolchildren in a comparable age group. The high prevalence of goiter could be explained on the basis of common environmental exposure to goitrogens and/or genetic factors. Among the 71 index cases, overt hypothyroidism was seen in 17% and subclinical hypothyroidism in 32%. Group 1 siblings had a 23% incidence of subclinical hypothyroidism and no overt cases were reported.

Thyroid Development and Function as Related to Etiopathogenesis of Thyroid Function

Advances in several aspects of thyroid gland development and function in past few decades have contributed to greater understanding of etiopathogenesis of thyroid disease in infancy and childhood. The human thyroid originates embryologically from an evagination of the pharyngeal epithelium with cellular contributions from the lateral pharyngeal pouches, followed by a process of descent to the neck with occasional persistence of the remnants along the tract as ‘lingual thyroid’, ectopic thyroid, thyroglossal cyst or nodules. Occasionally, lingual thyroid may be the sole functioning thyroid tissue which may not maintain optimal euthyroid status. Three transcription factors, TTF-1, TTF-2 and PAX8, are important for thyroid gland morphogenesis and differentiation. Other genes (HOX genes) regulate the expression of PAX-8 and TTF-1. Embryogenesis and biochemical maturation of the thyroid gland and the pituitary is largely complete by 10-12 weeks and thyroglobulin can be detected in follicular cells with evidence of iodine uptake and organification. T4 and T3 are detectable in fetal serum by 10-12 weeks with progressive increase in their levels. A transcription factor, Pit-1 is important for growth and differentiation of pituitary thyrotrhops which play an important role in regulating thyroid gland development and function. This abnormality causes central (pituitary / hypotalamic) hypothyroidism. Faulty embryogenesis can lead to thyroid dysgenesis (aplasia, hypoplasia, ectopia) which is the major underlying cause of hypothyroidism in infancy and early childhood and involves nearly 75% of newborns and infants with congenital primary hypothyroidism (CH). It is usually non-genetic but the underlying cause remains enigmatic. The thyroid gland concentrates iodide from blood and synthesizes and secretes thyroxine (T4) along with smaller amount of 3,3’5-tri-iodothyronine (T3). Deficiency of iodine in various regions of endemic iodine deficiency is an important cause of endemic cretinism and subnormal mental development. It is considered one of the most economical and easily preventable nutritional disorders. The synthesis and secretion of thyroid hormones occurs through a series of enzyme dependant steps. The thyroglobulin so formed is stored in colloid, functioning as a thyroid hormone precursor releasing thyroid hormones in circulation as required and also permitting storage of iodine. Inherited inborn errors of metabolism with autosomal recessive transmission, lead to biosynthetic defects of thyroid hormone production (dys hormonogenesis) usually leading to familial goitrous hypothyroidism involving other siblings. T4 and T3 circulate bound to transport proteins – the thyroxine binding globulin (TBG), albumin and transthyretin. The transport carrier proteins though nonessential for normal thyroid function, serve as extrathyroidal storage pool of thyroid hormone, releasing the free hormone on demand and protecting tissues from ill effects of elevated levels. TBG deficiency (incidence 1:5 to 8000), because of low circulating total T4 levels can lead to a mistaken diagnosis of hypothyroidism in newborns screened for CH; normal thyroid stimulating hormone (TSH) and
Physiologic Changes in Thyroid Hormone in the Neonate

During fetal life there is a progressive increase in circulating T4 and rT3 but T3 tends to be low (fetal protective measure) and may be in hypothyroid range at birth. It is important to be aware of the physiological variations in the levels of TSH and circulating thyroid hormones which occur soon after birth. There is an acute surge in the TSH level within 30 minutes of birth which is followed by rise in serum T3 and T4 levels by 24 hours, with a gradual decline in their levels as well as that of TSH and rT3 by end of first week. TSH surge in the premature infant is of a lesser magnitude with a greater decline in T4 concentration in the following 2 weeks. These physiologic changes have helped determine the timing (at birth from cord blood, or heel prick 2-5 days) and the source of blood collection (chord blood or heel prick) in neonatal screening programmes for CH. Most screening protocols use filter paper TSH or T4, or less commonly both TSH and T4 as well as T3. Appropriate interpretation of TSH, T3, T4 values is extremely important in arriving at the correct diagnosis when newborns are screened for congenital hypothyroidism, with due attention to gestational age, fetal and maternal health status and medications. Neonatal screening for CH which is the most cost effective of all neonatal screening programmes is usually performed within 3 to 5 days of birth by heel prick, when TSH and T4 levels are expected to normalize or from cord blood (placental end of cord) as soon as baby is delivered. Based on data compiled over the past 4 decades majority of newborns have TSH values less than 20 µIU/ml or < 10 (with the newer assays) while as 90% of them having CH have TSH > 50 µIU/ml, T4 levels tend to be above 6 µg/dl in normal term newborn infants. Levels of TSH more than 20 µIU/ml or T4 levels below 6 µg/dl in a full term infant should arouse suspicion and need to be rechecked within a week. If feasible thyroid USG (by an experienced sonologist) or Tcm99 scan should be performed if the TSH remains higher or T4 is low. Imaging studies even in a confirmed case of CH are useful to determine the underlying cause of CH, whether it is thyroid dysgenesis or dysmorphogenesis. During infancy TSH levels upto 10µIU/ml are considered normal provided serum T4 levels are in normal range. Circulating levels of T3 and T4 are maintained higher during infancy and early childhood hence age appropriate standard charts should be used for correct interpretation. The mean total T4 and T3 levels + 2 SD during infancy are 10.5µg/dl (7.5 to 15.5) and 1.68ng/ml (1.13 to 2.44) respectively, between 1 to 5 years of age mean levels are 10.5 µg/dl and 1.65ng/ml and between 5 to 10 years of age 9.3 µg/dl and 1.50mg/ml respectively. TSH beyond infancy is maintained within the usual 0.3 to 0.5 to 5µIU/ml. Thus, while treating a hypothyroid child maintenance of serum T4 levels in upper normal range is important with TSH in the normal range. As stated earlier thyroid hormone actions also vary with age, with maximal effects on somatic, skeletal growth and maturation, brain growth and development in infancy and childhood. Thyroid also influences the onset and progression of normal sexual maturation, Puberty may be delayed or occasionally precocious in children with hypothyroidism. Adequate understanding of etiopathogenesis of thyroid disease is enhanced by appreciation of the developmental biology of thyroid gland and H-P-T axis. As hypothyroidism is the most frequent thyroid disease encountered in pediatric age group with consequences which can be life long, it is discussed in detail.
Transient Hypothyroinemia

It is seen to some extent in many preterm infants. Immaturity of the hypothalamic-pituitary axis may be physiologically normal for the infant’s gestational age. Preterm serum T₄ and FT₄ concentrations are lower than those of term infants, but the TSH concentrations are comparable to term infants. In preterm infants, serum TBG were found to be only marginally low and do not correlate with the degree of hypothyroinemia. As a result, the FT₄ is rarely as low as the total T₄. Serum inhibitors of T₄ binding, present in many patients with non-thyroidal illness, may be an additional contributor to the decreased T₄ values. The presence of midline facial abnormalities, hypoglycaemia, microphallus, or visual abnormalities should prompt one to exclude the possibility of a hypothalamic-pituitary abnormality before considering hypothyroinemia. Septo-optic dysplasia, often associated with pituitary hormone deficiencies, can manifest as central hypothyroidism. Genetic mutation in HESX-1 has been described in septo-optic dysplasia. Clinical symptoms of hypopituitarism, such as neonatal hypoglycaemia (from growth hormone and adrenocorticotropic hormone deficiencies), polyuria (from anti-diuretic hormone deficiency), or small phallicus in boys (from gonadotropin deficiencies), along with the presence of blindness, congenital nystagmus, or midline defects of the brain, should alert the physician to suspect the diagnosis of septo-optic dysplasia. Alternatively, multiple pituitary hormone deficiencies suggest a genetic defect in the cascade leading to lethal pituitary formation, such as PROPI, LHX3, and POU1F1. DNA screening for these molecular abnormalities could be beneficial in the future for the rapid and accurate detection of these affected infants during the first weeks of life, but is not yet available clinically. Isolated TSH-releasing hormone (TRH) deficiency may cause low-normal T₄ and low or normal TSH concentrations. Secondary (or central) hypothyroidism may be suspected in infants with low T₄ and FT₄ and low TSH concentrations. Mutations have been identified in the β subunit of TSH, TRH gene, and TRH receptor gene. Congenital TSH and growth hormone deficiencies may occur in consequence to a difficult birth or anoxia.¹

Hypothyroidism in Infancy and Childhood

Etiology

Primary hypothyroidism due to thyroid dysgenesis is the most common thyroid dysfunction seen in childhood. Autoimmune thyroid disease (chronic lymphocytic thyroiditis – CLT) is the other important cause of hypothyroidism acquired later in childhood. Pituitary or hypothalamic disease can cause secondary or tertiary forms of hypothyroidism which may be congenital or acquired following intracranial disease. It is usually associated with deficiency of other pituitary hormones.² Worldwide prevalence of congenital hypothyroidism approximates 1:3500 to 4000 newborns as revealed by neonatal screening programmes implemented in several parts of the world with racial and ethnic differences in its incidence. It is twice as common in females. Our earlier data on neonatal screening of 40,000 newborns indicated higher incidence of nearly 1:2,500 to 1:2,800, but it could be even higher. Most of the infants detected on screening are asymptomatic in the first few weeks of life, thus fulfilling one of the major objectives of screening which is to detect asymptomatic infants and treat them very early so as to prevent or minimize intellectual impairment and neuropsychologic damage which can be irreversible when the treatment is delayed beyond the first few weeks of life. Inherited biosynthetic defects (dyshormonogenesis) with autosomal recessive transmission leading to goitrous hypothyroidism has a reported incidence of 10 to 15% of children with CH, but nearly 19 to 20% in our experience.³ Siblings are also affected hence family study is important. Autoimmune thyroid disease (CLT) causing hypothyroidism is common beyond mid-childhood and in adolescents and discussed later. Endemic iodine deficiency still remains an important cause of endemic cretinism and hypothyroidism in some parts of the world and in sub Himalayan regions of India. CLT which is the most common cause of hypothyroidism in pediatric age group beyond 5 years of age deserves special mention. CLT, an auto-immune disease is closely related to Graves’ disease. In both CLT and Graves’ disease, an inherited predisposition to autoimmunity and additional environmental and hormonal factors trigger and modulate the disease process. In CLT, lymphocyte and cytokine-mediated thyroid destruction predominates whereas, in Graves’ disease, antibody-mediated thyroid stimulation occurs but overlap may occur in some patients. Both goitrous (Hashimoto’s thyroiditis) and non-goitrous (primary myxedema) variants of thyroiditis have been distinguished. The disease has a striking predilection for females and a family history of autoimmune thyroid disease (both CLT and Graves’ disease) is found in up to 40% or more of patients. The common age at presentation is beyond mid childhood and adolescence but the disease may occur even in infancy. Patients with insulin-dependent diabetes mellitus, 20% of whom have positive thyroid antibodies and 5% have an elevated serum TSH level, have an increased prevalence of CLT, which may also occur as part of an autoimmune polyglan- dular syndrome.¹¹ The incidence of CLT is increased in patients with Turner, Down and Klinefelter syndromes. When stimulatory TSH receptor antibodies are present, they may give rise to a clinical picture of hyperthyroidism, the co-existence of CLT and Graves’ disease being known as hashitoxicosis. Blocking antibodies, on the other hand, have been postulated to underlie both, hypothyroidism and the absence of goiter in some patients with primary myxedema but are detectable in only a minority of children. In rare instances, the disappearance of blocking antibodies has been associated with normalization of thyroid function in previously hypothyroid patients. Goiter, which is present in approximately two-thirds of children with CLT, results primarily from lymphocytic infiltration and, from a compensatory increase in TSH. Children with CLT may be euthyroid or may have compensated or overt hypothyroidism, rarely an initial thyrotoxic phase is noted which occurs due to the discharge of preformed T4 and T3 from the damaged gland. Alternatively, thyrotoxicosis may be due to concomitant thyroid stimulation by TSH receptor stimulatory antibodies (hashitoxicosis). Children with thyroid hormone resistance constitute a rare cause of hypothyroidism. There may be selective pituitary resistance as distinct from generalized resistance to thyroid hormone. They come to attention when thyroid function tests are performed because of poor growth, hyperactivity, a learning disability or other non-specific signs or symptoms or a small goiter. The presentation is highly variable because of genetic heterogeneity. Individuals may be asymptomatic, or may have symptoms of thyroid hormone deficiency or excess. Thyroid hormone resistance is almost always due to a mutation in the TRβ. There may be involvement of the thyroid gland in generalized infiltrative (cystinosis), granulomatous (histiocytosis X), mitochondrial disease or infectious disease processes. Mantle irradiation of the neck for Hodgkin disease or lymphoma or craniospinal irradiation can also result in primary hypothyroidism. Family history of sibling affection can
often be elicited in presence of goitrous hypothyroidism due to
dysshormonogenesis. In children with autoimmune thyroiditis
elders often have thyroid disease both hypothyroidism and
thyrotoxicosis and familial or community prevalence may be
also be evident in endemic iodine deficiency. 12

Clinical manifestations

The symptoms and signs of congenital hypothyroidism in
the neonatal period are nonspecific and vague, leading
to difficulties in clinical diagnosis with less than 10% of
newborns detected on screening being recognized clinically.
Symptoms often predominate over signs. Growth retardation
so characteristic of this disorder in postnatal life is not seen
at birth. These infants may be large at birth and may be post
mature. Congenital hypothyroidism should be suspected when
4 or 5 early manifestations are present. These include prolonged
physiological jaundice, constipation, feeding difficulties,
inactivity, macroGLOSSIA, constipation, wide fontanelles,
mottling, hypoMENAL and hoarse cry. Coarse hypothyroid
facies, puffiness of eyes, protruding tongue, pallor, lethargy,
altered skin and hair texture, hypotonia, distended abdomen
with umbilical hernia, low pitched irritable prolonged cry, all
these give a characteristic appearance to these infants4. Other
helpful signs are bradycardia, muffled heart sounds, delayed
relaxation while eliciting deep tendon reflexes. Failure to grow
and delayed milestones become increasingly obvious. Children
with dysshormonogenesis may present with goiter at birth or
during infancy. The incidence of other associated congenital
abnormalities with CH is around 8%. Hypothyroidism in
older children is usually caused by autoimmune thyroiditis but
occasionally children with thyroid dysgenesis having
hypoplastic or ectopic thyroid tissue or dysshormonogenesis may
present late. Subtle signs of hypothyroidism in older children
may be difficult to appreciate clinically but failure to grow
or short stature of insidious onset and lethargy should raise
suspicion. Presence of a small goiter which is firm in consistency
with a pebbly surface favours the possibility of thyroiditis as
opposed to dysshormonogenesis where the goiters may be
small or large but the consistency tends to be usually soft with
occasional presence of a bruit. Congenital hypothyroidism can
also present as obesity, goiters, scholastic problems, delayed
sexual maturation or uncommon sexual precocity or muscular
hypertrophy. 13

Diagnosis

- The diagnosis of primary hypothyroidism is confirmed by
  the presence of low serum T4 and T3 concentrations and
  elevated serum TSH values. Estimation of free T4 and free
  T3 is also available now.
- TSH is an extremely sensitive index of primary
  hypothyroidism.

Low T4 and elevated TSH values

Any infant with a low T4 concentration and TSH
concentration greater than 40µIU/L is considered to have
primary hypothyroidism. Such infants should be examined
immediately and have confirmatory serum testing performed to
verify the diagnosis. In infants with primary hypothyroidism,
replacement treatment with levothyroxine should be started
immediately following confirmatory tests even before the results
of these tests become available. In cases with a screening TSH
concentration only slightly elevated but lower than 40µIU/L, a
second screening test should be performed using new fresh blood
sample obtained on a filter-paper. TSH values lie between 20
and 40 mU/L in nearly 10% of infants with confirmed CH. The

age appropriate normative values should be used as reference. During the most common time of reevaluation (between 2 and
6 weeks of age), the reference range for TSH is 1.7 to 9.1mU/L.

Normal T4 and elevated TSH values

Hyperthyrotropinemia is characterized by elevated serum
TSH concentrations during the neonatal period despite normal
T4 and FT4 concentrations. Hyperthyrotropinemia can be a
permanent or transient thyroid abnormality or may involve
delayed maturation of the hypothalamic-pituitary axis. There
may be compensated, mild (subclinical) primary hypothyroidism
due to inactivation mutations of the TSH-R in the neonatal
period. Neonates with Down’s syndrome have a higher incidence
of both transient and persistent hyperthyrotropinemia and CH.
Transient neonatal hyperthyrotropinemia may persist till age 10
or later in some cases. 14

Low T4 and normal TSH values

Thyroid insufficiency is defined to occur when infants have
normal TSH but low T4 values (defined as 2 SDs below the
mean for the reference range for age, usually below 10µg/dL
in the newborn infant). The low T4 with normal TSH profile
is seen in 3% to 5% of neonates. This pattern may result from
hypothalamic immaturity (particularly in preterm infants, 12%
of all newborn infants). Low T4 but normal TSH results are also
observed during illness, with protein-binding disturbances
such as TBG deficiency (1 in 5000), in central hypothyroidism
(1 in 25000 to 1 in 50000 newborn infants; see next 3 paragraphs),
or with primary hypothyroidism and delayed TSH elevation (1
in 10000 newborn infants). Newborn infants who are preterm
or ill are found with disproportionate frequency among those
with this set of laboratory values. In neonates/infants, inhibition
of TSH (causing low T4 concentrations) can result from constant
infusions of dopamine or high-dose glucocorticoids. Isolated
TSH-releasing hormone (TRH) deficiency may cause low-normal
T4 and low or normal TSH concentrations. Secondary (or central)
hypothyroidism may be suspected in infants with low T4 and FT4
and low TSH concentrations. Mutations have been identified in
the β subunit of TSH, TRH gene, and TRH receptor gene. Finally,
congenital TSH and growth hormone deficiencies may occur as
a result of a difficult birth or anoxia.

Low T4 and delayed TSH increase

Many infants with low T4 concentrations and normal TSH
values on initial screening (1 in 100000 newborn infants) who are
subsequently found to have an elevated TSH concentration are
LBW, VLBW, or critically ill preterm and term neonates. Serum
TSH values in these infants increase during the first few weeks of
life to concentrations characteristic of primary hypothyroidism.
It is unclear whether infants with this delayed TSH elevation
have an abnormality of pituitary-thyroid feedback regulation,
transient hypothyroidism (e.g. iodine induced), or a mild form
of permanent congenital hypothyroidism (CH). Long-term
follow-up of these infants has not been reported. It is important,
therefore, that serum FT4 and TSH be tested in infants with
overly low T4 concentrations or in any infant with suggestive
signs of hypothyroidism. Infants with low T4 and a delay in
elevation of TSH values and those with normal T4 concentrations
and elevated TSH values might be missed on initial screening.
Neither a primary T4/backup TSH nor a primary TSH/backup
T4 screening strategy will detect the rare infant with a normal T4
at birth but delayed TSH increase. Five per cent to 10% of LBW
and VLBW infants with CH may have normal screening hormone
concentrations even in the absence of technical and human errors
and regardless of the approach used. 13-15

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TSH. The preferred preparation is sodium-levothyroxine level in the upper normal range and normalize the elevated complete evaluation. For a period of about 6 to 8 weeks and restarted if needed after can be continued for the initial 3 years when it can be omitted stressed. In case the diagnosis is not beyond doubt therapy in congenital hypothyroidism should be adequately

Treatment and monitoring

Goal of therapy

Thyroid ultrasonography and/or thyroid scan (see text for recommendations)

Monitoring

Recheck serum TSH and FT4

Recheck T4, TSH

2–4 wk after initial treatment is begun

Every 1–2 mo in the first 6 mo

Every 3–4 mo between 6 mo and 3 y of age

Every 6–12 mo from 3 y of age to end of growth

Breastfeeding can continue. Only T4 tablets should be used. In newborns detected on screening and in early infancy, 10 to 15µg/kg has been recommended. Per kg dose often declines with age upto 8 to 6µg/kg during late infancy and early childhood, 6 to 4µg/kg in later childhood and 4 to 2µg/kg in adolescents. The daily requirement is about 100µg/m2 but therapy needs to be individualized. In newborn period, full replacement therapy can be initiated promptly. In longstanding thyroid deprivation of whatever underlying cause, where the diagnosis is delayed for months or occasionally for years, smaller doses upto quarter of the daily dose can be administered initially and stepped up gradually to full replacement dose, in 4 to 6 weeks.16

The required dose is administered as one single dose, preferably at a convenient fixed time during the day usually first thing in the morning, on empty stomach to maximize absorption. Regular therapy is extremely important.

Individualization of therapy by monitoring serum thyroid levels and TSH is ideal and necessary. Therapeutic monitoring is recommended with blood samples obtained at periodic intervals for TSH and T4 estimations, more frequently in infancy, initially after 4 weeks of initiating therapy and subsequently 2 monthly during infancy, about 3 monthly during first 3 years of life and 4 to 6 monthly in older children and also within 6 to 8 weeks of any change in the dose. Clinical evaluation and growth monitoring during therapy are important. While most children with CLT who are hypothyroid initially remain hypothyroid, spontaneous recovery may occur, particularly in those with initially compensated hypothyroidism. On the other hand, some initially euthyroid patients specifically those with elevated thyroid antibodies (TPO) become hypothyroid later, whether or no treatment is initiated. Clinical and laboratory follow-up is advisable.17

During therapy, the serum total T4 or FT4 should and might be in the upper half of the reference range (target values depend on the assay method used [T4: 10–16µg/dL (130–206nmol/L); FT4: 1.4–2.3ng/dL (18–30pmol/L)]) during the first 3 years of life with a low-normal serum TSH. The latter may sometimes be delayed because of relative pituitary resistance. In such cases, characterized by a normal or increased serum T4 and an inappropriately high TSH concentration, the T4 value is used to titrate the dose. The most frequent cause of persistent TSH elevation is poor compliance and should be excluded first. Infants with low serum T4 concentrations (below 10µg/dL [129nmol/L]) and a TSH concentration greater than 15mU/L during the first year of life are at risk of having lower IQ values than patients whose T4 concentrations are constantly controlled at higher concentrations. Subsequently, thyroid function test values should be kept at age-appropriate levels in children, which are different from those for adults. On TH-replacement therapy, TSH levels should be maintained between 0.5 and 2.0mU/L during the first 3 years of life.

During the first three years of age, the physician should conduct clinical evaluation of the infant at frequent intervals. Initial and ongoing counseling of parents is extremely significant to emphasize the importance of major sequelae that may occur
Fig. 1: Neonatal screening programme for CH

Monitoring
Clinical examination, including assessment of growth and development, should be performed every few months during the first 3 years of life. Infants with CH appear to be at increased risk of other congenital anomalies (approximately 10% of infants with CH, compared with 3% in the general population). Cardiovascular anomalies, including pulmonary stenosis, atrial septal defect, and ventricular septal defect, are the most common. Frequent laboratory and clinical evaluations of thyroid function, growth, and development should be carried out in infants to ensure optimal T4 dosage and adherence to therapy.

- At 2 and 4 weeks after the initiation of L-T4 treatment
- Every 1 to 2 months during the first 6 months of life
- Every 3 to 4 months between 6 months and 3 years
- Every 6 to 12 months until growth is completed; and
- At more frequent intervals when compliance is questioned, abnormal values are obtained, or dose or source of medication has been changed; FT4 and TSH measurements should be repeated 4 weeks after any change in L-T4 dosage.

The aim of therapy is to ensure normal growth and development by maintaining the serum total T4 or FT4 concentration in the upper half of the reference range in the first year of life, with a serum TSH in the reference range (optimally 0.5–2.0mU/L). Some infants will have serum TSH concentrations in the range of 10 to 20mU/L despite T4 concentrations in the upper half of the reference range. Elevated TSH relative to the FT4 is hypothesized to occur as a result of in utero hypothyroidism in rare cases. This produces a resetting of the pituitary-thyroid feedback threshold. A failure of the serum FT4 concentration to increase into the upper half of the reference range by 2 weeks and/or failure of the TSH concentration to decrease to less than 20mU/L within 4 weeks after initiation of L-T4 administration should alert the physician that the child may not be receiving adequate L-T4. Consequences of hypothyroidism acquired beyond the age of 3 to 4 years differ from CH as stated earlier, because of poor compliance and noncompliance. 18

**Prognosis and Outcome**
The outcomes of patients with CH is closely dependent upon the nature and severity of the underlying thyroid abnormality, the age at diagnosis and onset of treatment, the adequacy and regularity of therapy and compliance with the required degree of clinical and laboratory follow-up. Worldwide neonatal screening programs for CH have had a significant impact on reducing intellectual deficits in hypothyroid infants diagnosed and treated early. Consequences of hypothyroidism acquired beyond the age of 3 to 4 years differ from CH as stated earlier,
but are influenced by factors similar to that in CH. Mental consequences are much less marked but behaviour alterations are noted with institution of therapy.

**Recommendation of the 2006 American Academy of Pediatric Guidelines**

- Every newborn infant should be tested before discharge from the nursery.
- Due to the elevated levels of TSH shortly after birth, results of screening of specimens taken within the first 24 to 48 hours of life occasionally are falsely positive for primary hypothyroidism (using TSH as the primary screen).
- It is better to screen before hospital discharge or before transfusion than missing the diagnosis of hypothyroidism. It should be kept in mind that screening very sick newborns or after transfusion may give false negative results.

It is recommended to collect the blood when the infant is between 2 and 4 days of age, but in certain situations, this is virtually impossible. In infants discharged from the nursery before 48 hours of age, blood should be obtained before discharge. Blood should be obtained by 7 days of age in cases such as home births or in the case of a critically ill or preterm neonate. It should be recognized that samples obtained after 4 days of age are late for screening of congenital adrenal hyperplasia or metabolic disease. Particular care must be taken with infants in neonatal intensive care units (NICU). In infants in the ICU, attention to urgent medical problems may result in missed newborn screening. When an infant is transferred to another hospital, the first hospital must indicate whether the specimen has been collected. The second hospital should obtain a specimen if there is no proof that blood was collected before the transfer.

Early thyroid scanning of infants with suspected hypothyroidism is controversial with regards to the risk-benefit ratio.

For physicians who opt for imaging, the benefits can be summarized as follows:

- If an ectopic gland is demonstrated, a permanent form of thyroid disease and CH has been established.
- The absence of thyroid gland uptake is most often associated with thyroid aplasia or hypoplasia. In the setting of an absent radiiodine uptake but normal gland on ultrasonographic examination, a TSH-R defect, iodine-transport defect, or maternal transfer of TRBAb should be considered.
- Normal scan findings (or a goiter) indicate a functioning thyroid gland with regard to iodine uptake and alert the physician to a probable hereditary defect in T4 synthesis. Measurement of serum thyroglobulin will help to separate thyroglobulin synthetic defects from other causes of hypothyroidism. Exposure to goitrogens other than iodine, such as anti-thyroid drugs produces a similar picture. Finally, some infants exposed to maternal TRBAb may have a normal scan if their hypothyroidism is partially compensated. Genetically mediated thyroid synthetic enzyme defects can be passed on to future generations and their identification is especially important for families planning on having additional children. In such cases, the physician can arrange for genetic counseling after scans are available.

- Some infants having a transient form of hypothyroidism may have normal scan findings at birth and do not fall into one of the above categories. Such infants should be carefully evaluated after 3 years of age, when discontinuing treatment temporarily is relatively safe as described under the conditions in “Assessment of Permanence of Hypothyroidism.”

Treatment need not be delayed to perform the scan. Elevated TSH found in patients with permanent CH rarely normalizes within the first few days of treatment, allowing a thyroid scan to be performed during this time. Serum TSH should be assessed at the time of the scan. If due to levothyroxine therapy, the TSH concentration becomes <30mU/L, ultrasonography can still be performed. A scan can be performed after the child reaches 3 years of age; at this time TH treatment can be interrupted without danger to the developing central nervous system. The usual dose of 125I, the preferred isotope, is 0.925MBq (25µCi). This represents a small amount of radiation exposure, equivalent to the amount of exposure with 2 to 3 chest radiographs. However, while performing the scan, the radiation dose and type should be taken into account. When large doses of isotope are administered or if 131I is used, the radiation exposure is potentially 100 times. Therefore, the procedure should be performed by well-experienced personnel using optimal equipment and using the minimally recommended tracer dose.

**Assessment of permanent hypothyroidism as per the American Academy of Pediatrics 2006 recommendations:**

- If the thyroid scan reveals an ectopic gland, or absent thyroid tissue (that is confirmed by ultrasonographic examination), or if the serum TSH rises above 10mU/L after the first year of life presumably because of insufficient T4 replacement, CH is considered permanent.
- If the scan does not reveal any permanent cause of CH or there’s no TSH increase after the newborn period, levothyroxine administration should be discontinued for 30 days at some point after the child is 3 years of age. After 30 days, serum should be obtained for measurement of FT4 and TSH values. It is critical that this follow-up laboratory assessment be obtained in a timely manner and that there be no loss of follow-up. However, if TSH is elevated with low FT4 levels, permanent hypothyroidism is confirmed and TH therapy should be reintroduced.
- If the FT4 and TSH concentrations remain in the reference range, euthyroidism is assumed and a diagnosis of transient hypothyroidism recorded. It is important that the child not be lost to follow-up. The physician should monitor the child carefully and repeat the thyroid function tests at the slightest suspicion of recurrence of hypothyroid symptoms. If the results are inconclusive, careful follow-up and subsequent testing will be necessary.
- More severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days. An alternative option is to reduce the TH-replacement dosage by half. If after 30 days the TSH is elevated above 20mU/L, the permanence of hypothyroidism is confirmed and full replacement therapy should be resumed. If the serum TSH value has not increased, then TH treatment should be discontinued for another 30 days with repeated serum FT4 and TSH determination as described above.

**Conclusion**

There is a high risk of development of autoimmune thyroiditis.
in family members of children with lymphocytic thyroiditis in India. If only one modality (i.e., thyroid antibody assessment or FNAC) is used to diagnose autoimmune thyroiditis in children, between 22%-33% of subjects are likely to be missed. There is a high prevalence of thyroid dysfunction among parents (fathers, 22%; mothers, 42%) and siblings. It is advisable for first-degree relatives of subjects with juvenile autoimmune thyroiditis, to undergo screening using serum TSH level estimation. Screening programs (in which specimens have been obtained at 4 to 6 weeks) have indicated that 10% of hypothyroid infants with T4 values in the normal range and elevated TSH values or with initially low TSH values were missed during initial screening. It is therefore, established that infantile hypothyroidism can still develop even when the screening T4 value is reported to be normal. Repeat testing should be done on serum during infancy whenever there is a clinical suspicion of hypothyroidism or when there is a family history of thyroid disease in pregnancy or familial thyroid dyshormonogenesis. A high index of suspicion, early diagnosis, timely intervention with adequate treatment, periodic therapeutic monitoring and counseling may help mitigate adverse effects and ensure optimal outcome. Screening for CH is the most cost effective screening procedure available till date. Adequate appreciation of the importance of thyroid function during these formative years of life provides greater insight and understanding of thyroid diseases in this age group. In infants and children thyroid diseases have far reaching effects on growth, development, maturation as well as cognitive skills and intellect. Efforts are ongoing to establish the optimal therapy that provides maximum potential for normal development for infants with congenital hypothyroidism. Recent Indian data has provided reference ranges for thyroid hormones in healthy school aged children.2524

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