Review Articles

Congenital Hypothyroidism – An Update
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Abstract
Hypothyroidism is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. The most cases of congenital hypothyroidism (CH) is from thyroid dysgenesis. The worldwide incidence CH is 1:3000-4000 live births and prevalence rate of CH in Bangladesh is 0.9%. The thyroid gland is the first endocrine structure in fetus. Triiodothyronine (T3) and thyroxine (T4) appear by 12 weeks of gestation. CH is classified into permanent and transient. Permanent CH requires life-long treatment. Common symptoms of CH are feeding difficulty, prolonged jaundice, lethargy, constipation and not growing well. Newborn with CH will have puffy face, wide posterior fontanelle, wide open sutures and later on umbilical hernia, coarse facies, macroglossia and cold or mottled skin are common signs. Measurement of T4 and TSH as newborn screening are appropriate approach with interpretation of T4 below 10th centile or TSH above 90th centile or absolute cut-offs such as T4 < 6.5 ug/dL and TSH > 20mu/L. The diagnosis of primary CH is confirmed by the finding of an elevated serum TSH level and a low free T4 or total T4. Early T4 replacement in children with CH is crucial for neurological outcome. A high starting dose of 10–15 ìg/kg/day is recommended by AAP and European Society for Paediatric Endocrinology (ESPE). The T4 levels normalize in first 3 days of initiation of treatment, while TSH levels take up to 1 month for normalization. Routine follow-up with biochemically adjustment of doses of L evothyroxine can completely normalize the children of CH.

Key words: Thyroid gland, Hypothyroidism, Thyroxin, TSH

Introduction
Hypothyroidism, also called underactive thyroid or low thyroid, is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone1. This disorder may be manifested from birth (congenital) or acquired. Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis and some cases are familial2. Most infants with congenital hypothyroidism are detected by newborn screening programs in the first few weeks after birth, before obvious clinical symptoms and sign develops.

Epidemiology
The incidence varies by geographic location. The worldwide incidence is 1:3000-4000 live births and in India it is 1:2500-2800 live births.1 One small study done at institute of nuclear medicine, Dhaka shows that prevalence rate of CH in Bangladesh is 0.9%,5,6 The incidence was somewhat lower in Whites (1:1815) and Blacks (1:1902), and highest in the Asian population (1:1016). Older mothers (>39 years) had a higher incidence (1:1,328) compared to younger mothers (< 20 years, 1:1,703). It was higher in preterm vs. term infants.3 Nearly all screening programs report a female preponderance, approaching 2:1 female to male ratio.4

Thyroid gland development in fetus
The thyroid gland is the first endocrine structure appearing during development. The median thyroid...
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Classification
Congenital hypothyroidism is classified into permanent and transient CH. Permanent CH refers to a persistent deficiency of thyroid hormone that requires life-long treatment. Transient CH refers to a temporary deficiency of thyroid hormone, discovered at birth, but then recovering to normal thyroid hormone production. Permanent CH can be further classified into permanent primary and secondary (or central) CH. In addition, some forms of CH are associated with defects in other organ systems; these are classified as syndromic hypothyroidism.

Etiology
In the majority of patients, CH is caused by an abnormal development of the thyroid gland (thyroid dysgenesis) which is usually a sporadic disorder and accounts for 85% of cases. It presents in three major forms i.e. thyroid ectopy, athyreosis and thyroid hypoplasia. Thyroid ectopy accounts for two thirds of cases of thyroid dysgenesis and is twice more common in females. The exact etiology of thyroid dysgenesis is not known. However; mutations in transcription factor genes that regulate thyroid gland development [thyroid transcription factor 2 (TTF-2), NKX2.1, also termed TTF-1] or PAX-8 would explain these defects. But, only 2% of cases with thyroid dysgenesis are found to have such genetic mutations.

For the remaining one-third of cases, CH results from absence of thyroid (athyrosis) and thyroid hypoplasia. Hereditary inborn errors in the enzymatic cascade of thyroid hormone synthesis, also called dyshormonogenesis, or to defects in peripheral thyroid hormone transport, metabolism, or action are accounted in approximately 15% of cases.

Secondary congenital (central) hypothyroidism may be isolated which results from mutation in thyroid stimulating hormone â (TSHâ) subunit gene or TRH receptor gene. More often it is associated with congenital hypopituitarism, which may be due to mutation in transcription factor gene regulating pituitary development i.e. HESX1, LH4X, PIT1 and PROP1. Transient CH in newborn may be due to maternal thyrotropin receptor-blocking antibodies, exposure to maternal antithyroid medications, iodine deficiency and iodine excess.

Symptoms
Symptoms of congenital hypothyroidism are initially non-descript; however, the maternal and pregnancy history may provide some clues. In twenty percent, gestation extends beyond forty-two weeks. One may also find evidence of maternal autoimmune thyroid disease or an iodine deficient diet. Inadvertent radioactive iodine treatment during pregnancy is rare. These babies are quiet and may sleep through the night. Additional symptoms include a hoarse cry and constipation. Neonatal hyperbilirubinemia for more than three weeks is common. This is due to immaturity of hepatic glucuronyl transferase. The most common symptoms were prolonged jaundice, lethargy, feeding difficulty and constipation.

Signs
The most common signs on initial examination are umbilical hernia, macroglossia and cold or mottled skin. Thyroid hormone is also important in the formation and maturation of bone.

Deficiency of this can lead to a wide posterior fontanel of greater than 5 mm. A few infants with congenital hypothyroidism may have a palpable goiter. This is usually found in thyroid dyshormonogenesis. The typical appearances of a hypothyroid infant include jaundice, a puffy face and a wide posterior fontanelle with open sutures. The nasal bridge is flat and the eyes exhibit pseudohypertelorism. The mouth may be slightly open revealing macroglossia. Further
examination would reveal bradycardia and a protuberant abdomen with a large umbilical hernia. Neurologic examination findings include hypotonia with delayed reflexes. Skin may be cool to touch and mottled in appearance reflecting circulatory compromise.11

**Diagnosis**

The diagnosis of CH is made after detection by NBS in most of the developed countries19. A complete diagnostic evaluation includes detection of CH by NBS, followed by confirmation by repeat thyroid function testing, and use of available modalities to determine the exact underlying etiology.

**Neonatal screening and confirmatory tests**

Blood from a heel prick (or cord) collected on special filter paper cards usually between 2 and 5 days of age is sent for either initial TSH or initial T4 test, with a follow-up TSH test according to the local NBS program.19 With either approach, a diagnosis is made in most infants with primary CH. Some NBS programs measure both T4 and TSH so as to not miss any cases with central CH, mild hypothyroidism, and those with delayed TSH rise.

Universal newborn screening is currently being done in many parts of the world including Asia (India), Western Europe, North America, Japan, Australia, and parts of Eastern Europe, South America, and Central America. Three approaches are being used for screening:20

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

Concomitant measurement of T4 and TSH is the most sensitive approach but incurs a higher cost. 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/L20).

It is now recognized that preterm infants or acutely ill term infants with primary hypothyroidism may not show an elevated TSH level on the 1st screening test. Thus, many programs undertake a routine 2nd screening test between two and six weeks of age in preterm and acutely ill term infants. Such testing leads to the detection of infants with “delayed TSH rise”, which occurs in approximately 1:18,000 newborns.21
Confirmatory serum thyroid testing

The diagnosis of primary CH is confirmed by the finding of an elevated serum TSH level and a low free T4 or total T4.

Subclinical primary hypothyroidism is diagnosed if free T4 or total T4 concentrations are normal, but TSH is elevated.22

A low T4, with either a low or an "inappropriately normal" TSH level confirms central or secondary CH. Infants diagnosed to have central CH must undergo evaluation for other pituitary hormone deficiencies.

Infants showing a low serum total T4, but a normal free T4 and normal TSH level may have TBG deficiency which can be confirmed by a low serum TBG level.22

Recent guidelines suggest immediate institution of therapy if venous TSH level is more than 20 mU/L or if venous free T4 levels are below norms for age.22 If free T4 levels are normal and TSH values range from 6 mU/L to 20 mU/L, a repeat evaluation is mandated after 3 weeks of age to reestablish abnormal T4 and TSH levels and to obtain a definitive diagnosis and decide about initiation of therapy.22 Most confirmatory serum tests are done after 2 weeks of life, when the upper TSH range falls to approximately 10 mU/L.

Abnormal values on screening should always be confirmed by a venous sample (using age appropriate cut-offs given in Table-1).

<table>
<thead>
<tr>
<th>Age</th>
<th>Free T4 (pmol/L)</th>
<th>Total T4 (nmol/L)</th>
<th>TSH (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 4 days</td>
<td>25 -64</td>
<td>129 -283</td>
<td>&lt; 39</td>
</tr>
<tr>
<td>2 -4 weeks</td>
<td>10 – 26</td>
<td>90 – 206</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

Diagnostic studies to determine an underlying etiology

Treatments of congenital hypothyroidism is based on serum thyroid function test results. Other diagnostic studies may be undertaken to determine an underlying etiology. It may include thyroid radionuclide uptake and scan, thyroid ultrasonography, serum thyroglobulin (Tg) measurement, antithyroid antibody determinations, and measurement of urinary iodine. However, these diagnostic studies generally do not alter the treatment decision, and so they are considered optional.

1. Thyroid ultrasonography

Thyroid ultrasonography is accurate in confirming true thyroid aplasia, presence of a thyroid gland in eutopic location. In the situations where radionuclide uptake and scan show absent uptake, but a gland is actually present (TSHâ gene mutations, TSH receptor inactivating mutation, iodide trapping defect, maternal TRB-Ab), ultrasonography may show a thyroid gland in a eutopic location. It also can confirm a large gland, suggestive of dyshormonogenesis.24

2. Thyroid radionuclide uptake and scan:

Radionuclide uptake and scanning generally are the most accurate tests in defining some form of thyroid dysgenesis, e.g. an ectopic gland, thyroid hypoplasia or thyroid aplasia.23 Either iodine-123 (I-123) or sodium pertechnetate 99 m (Tc99 m) are preferred for thyroid uptake and scan in neonate. Absence of radionuclide uptake should be confirmed by an ultrasonography.

3. Serum thyroglobulin (Tg) determination:

Serum thyroglobulin levels reflect the amount of thyroid tissue and generally are elevated with increased thyroid activity, as when TSH is elevated. Serum thyroglobulin determinations can be useful in cases of absent radionuclide uptake.25 If the thyroglobulin level is increased, this suggests that the thyroid gland is present.

4. Anti-thyroid antibodies:

Maternal autoimmune thyroid disease may be associated with production of a thryotropin receptor blocking antibody (TRB-Ab). In a case where a previous child has had transient congenital hypothyroidism, and mother has known autoimmune thyroid disease and is pregnant again TRB-Ab determinations can be done.23

5. 24-hour urinary iodine: This determination is undertaken if iodine excess or deficiency is suspected to be the cause of CH, which is transient in almost all cases. The normal level in neonates is 50–100ìg.

Treatment of CH

Timely initiation of T4 replacement in children with CH is crucial for neurological outcome. The goal of therapy is to achieve a growth and mental development close to the genetic potential of patients.

Levothyroxine is the treatment of choice. Treatment with only levothyroxine has been shown to normalize serum T3 and is considered sufficient.24
A high starting dose of 10–15 ìg/kg/day is recommended by the American Academy of Pediatrics and the European Society for Paediatric Endocrinology (ESPE).25

Treatment should be initiated in any infant (term as well as preterm infants with congenital hypothyroidism patient) with a positive screening result, right after confirmatory tests are drawn. The absorption of medication is best on empty stomach and may be impaired by gastrointestinal disorders like celiac disease, inflammatory bowel disease, lactose intolerance, Helicobacter pylori infection, and atrophic gastritis as well as drugs such as proton pump inhibitors, aluminum-containing antacids, sucralfate, cholestyramine and other resins, ferrous sulfate, calcium, phosphate binders, fiber supplements, and soy protein formulas.26 The T4 levels normalize in first 3 days of initiation of treatment, while TSH levels take up to 1 month for normalization even though a 50% decrease occurs in first 3–4 days.27

**Treatment Goals**

**Treatment Goal:**

The treatment goals as outlined by the American Academy of Pediatrics (AAP)28 are as follows:

- Serum Free T4 or total T4 should be kept in the upper range of normal during the first year of life.
- Target values during the first year are 130 to 206 nmol/L (10-16 ìg/dl) for the serum T4 and 18 to 30 pmol/L (1.4 to 2.3 ng/dl) for free T4.
- Serum TSH should be kept <5 mU/L.

**Recommended follow up**

Clinical evaluation should be performed every few months during the first three years of life along with frequent measurements of serum T4 or free T4 and TSH. The American Academy of Pediatrics recommends the following monitoring schedule28.

- At two and four weeks after the initiation of l-thyroxine treatment.
- Every 1-2 months during the first 6 months of life.
- Every 3-4 months between 6 months and three years of age.
- Every 6-12 months thereafter until growth is complete.
- Four weeks after any change in dose.

More frequently if results are abnormal or non-compliance is suspected.

All children confirmed to have permanent CH need lifelong treatment. Serial TSH values and need for increasing levothyroxine dose with age are indicators of permanence of CH.

In children suspected to have transient CH, a trial of discontinuation of therapy should be given at about 3 years of age or earlier to decide about further continuation of therapy.29, 30

**Outcome**

Factors known to influence the neurodevelopmental outcome in children with CH are the age at initiation of treatment, starting dose of levothyroxine, severity of hypothyroidism, serum T4 concentrations in the first 2 years of life, and compliance to therapy23. The dose and timing of levothyroxine therapy are crucial to the neurologic outcome in CH. Behavioral and cognitive testing scores are significantly lower when normalization of T4 takes more than 2 weeks31. Early diagnosis & adequate treatment from the first weeks of life result in normal linear growth and intelligence comparable with that of unaffected siblings.2 The scores on the mental development index (MDI) and verbal IQ were predicted by mean T4 and TSH during the first year of treatment. 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.32

Therefore it is important to closely monitor these infants and adjust the l-thyroxine dose frequently until the desired level is achieved.

**Conclusion**

Congenital hypothyroidism is the commonest preventable causes of mental retardation. But delay in diagnosis, failure to correct initial hypothyroxemia, inadequate treatment, and poor compliance in the first 2-3 yr of life result in variable degrees of brain damage. It is more prevalent in endemic goiter regions of Bangladesh. Magnitude of the problem should be studied further to improve the situation and neonatal screening program should be implemented as soon as possible at national level.
References


