



Guidelines for Management of Congenital Hypothyroidism

Summary

Please refer to the full Guidelines below for details.

1. Diagnosis

TSH assay is used as the primary newborn screening test for congenital hypothyroidism (CH).

2. Evaluation [Section 4]

All babies notified by the central laboratory need immediate evaluation (within 48 hours).

History and Examination

- Maternal: diet, history of drugs, auto-immune disease
- Baby: symptoms and signs of CH, jaundice, goitre, growth parameters, other congenital problems

Investigations

- Thyroid function tests (TFTs), consisting of thyroid stimulating hormone (TSH) and free thyroxine (FT4)
- Plasma bilirubin if indicated
- Thyroid scan using technetium99 or I123
- Xray of the knee for bone age (optional)
- Maternal and baby TSH receptor antibodies (or antithyroglobulin and antimicrosomal antibodies if former not available) where there is a positive maternal history of auto-immune thyroid disease

3. Treatment [Section 5]

- This should be started as soon as congenital hypothyroidism is confirmed on TFTs (preferably same day).
- Thyroxine is given at a dose of approximately 10 ug/kg/day.
- Thyroxine tablet is crushed and mixed with a little milk or water (prepared suspensions are not sufficiently stable).
- Dosage is adjusted according to TFTs aiming to keep the free T4 concentration at the upper end of the normal range and TSH suppressed into the normal range.

4. Follow-up [Section 7]

- Follow-up should occur at two weeks, six weeks, three months and then two to three monthly during the first year. Thereafter at three monthly intervals until two to three years, then four monthly.
- TFTs are repeated at each visit and dosage adjusted as above. TFTs may need to be performed more frequently if progress is not satisfactory.
- Growth and development must be closely monitored.



- Hearing tests at four to eight weeks and then three monthly for at least the first year in babies with dysghormonogenesis.
- Developmental assessment as clinically indicated (assessment at 18 - 24 months and pre-school are suggested useful times).
- Suspected transient congenital hypothyroidism should be tried off therapy at three years of age, or allowed to grow out of their dose.

1. CLASSIFICATION

Primary congenital hypothyroidism can be permanent or transient.

1.1 Permanent:

Dysgenesis (c. 80-90%)

Ectopic (45-50%)

Athyrotic (35-40%)

Dysghormonogenesis (10-20%) - includes Pendred syndrome

Other (c. 5%) - includes TSH receptor mutations

1.2 Transient:

Causes include: exposure of infant to iodine containing antiseptics, maternal factors such as antithyroid drugs, auto-immune thyroid disease, iodine excess/deficiency diets.

2. INCIDENCE

Incidence in Australia is about 1: 3,600 live births and in New Zealand 1: 4900 live births¹

3. NEWBORN SCREENING AND NOTIFICATION

Newborn screening is performed on all neonates at approximately two to five days after birth. In Australasia the primary screening test for congenital hypothyroidism is a TSH assay. This detects neonates with primary hypothyroidism but not those with a deficient TSH (2°/3° hypothyroidism). After birth, there is a physiological surge in TSH, which may be modestly elevated for the first few days².

If there is a borderline elevation of TSH on the first specimen, a repeat specimen is requested. All neonates with a significantly elevated TSH level in the first sample, or a persistently elevated level in the second sample need immediate further biochemical and clinical evaluation.

The levels at which the laboratory issues the notification as well as arrangements for evaluation differ among laboratories. There is immediate notification by phone to the responsible doctor, followed by a printed notification giving details of the mother and baby and screening results. It is requested that follow-up information regarding confirmatory thyroid function testing, diagnosis and treatment be filled in on the form and returned to the screening laboratory.



3.1 Low birth weight babies

In very low birth weight babies (particularly premature neonates) TSH screening should be repeated a few weeks after the initial specimen to detect those babies where immaturity of the hypothalamic-pituitary-thyroid axis may initially mask primary congenital hypothyroidism. It is recommended that the test be repeated two weeks after birth in babies 1000-1500g and at four weeks in those < 1000g.

4. EVALUATION

4.1 Maternal

Evaluation includes details of possible maternal thyroid disease/medications, details of maternal diet during pregnancy as well as any family history of thyroid disease or deafness (the latter suggestive of possible Pendred syndrome).

4.2 Infant

The baby needs to be evaluated as soon as possible, usually within 48 hours of notification. Where possible this is best achieved in a paediatric centre, appropriately equipped and with personnel experienced in differential diagnosis and management of cases of suspected congenital hypothyroidism. Clinical features suggestive of hypothyroidism on history and examination should be sought. Examine baby for goitre. Growth parameters (length, weight and head circumference) are particularly important for follow-up. There is a slightly increased chance of other congenital abnormalities in babies with CH (10% vs 3% in the normal newborn population). Congenital heart disease is the most common congenital abnormality, especially pulmonary stenosis, ASD, and VSD³.

Investigations

4.3.1 TSH and FT4

To confirm the results of newborn screening and to determine the degree of hypothyroidism

4.3.2 Plasma Bilirubin

To be done if the baby is significantly jaundiced

4.3.3 Thyroid Scan

This is strongly advised, as it usually gives clear-cut diagnostic information and allows the family to be given an explanation of the nature of their child's disorder. It also identifies those babies with possible dysmorphogenesis.

The thyroid scan is usually performed with technetium-99m (99mTc pertechnetate). The scan can be performed within a few days of starting therapy (up to five days) if there are difficulties with arrangements but treatment should not be delayed while waiting for a scan.

Thyroid scan is usually the investigation of choice. Ultrasound may occasionally be used to determine the presence of a thyroid gland when thyroid scan shows no uptake. This finding indicates the possible presence of blocking antibodies and transient hypothyroidism but does not change initial management.



Scan findings

1. Absent isotope uptake usually means agenesis of the thyroid gland but may be caused by maternal blocking antibodies.
2. Uptake may be reduced or in an abnormal position indicating a hypoplastic or ectopic gland.
3. Increased uptake in the normal position usually indicates an inherited defect of thyroxine biosynthesis, dyshormonogenesis, or excessive exposure to iodide. The gland is usually enlarged on scan and clinically.

4.3.4 XRay of the Knee

Absence of epiphyses may reflect the degree of intrauterine hypothyroidism⁴.

4.3.5 Maternal and Infant Antithyroid Antibodies

To be done if there is a history of maternal auto-immune thyroid disease. TSH receptor antibody measurement is preferable, but anti-thyroglobulin and anti-thyroid peroxidase antibodies may provide indirect evidence of maternally transmitted thyroid auto-immunity and should be ordered if a TSH receptor antibody assay is not available. If a maternal history of thyroid auto-immunity is known beforehand, it is suggested that TSH receptor antibodies be performed on the mother during pregnancy and on cord blood. High titres correlate with clinically significant neonatal disease.

4.3.6 Hearing Tests

To be organized for all babies with suspected dyshormonogenesis (family history of Pendred syndrome or thyroid scan findings as above). The sensorineural hearing loss of Pendred syndrome is associated with structural changes in the inner ear (Mondini malformation) and may fluctuate and deteriorate over time. Testing using auditory brain stem responses or oto-acoustic emissions is recommended at the age of four to eight weeks. Thereafter testing should be repeated three monthly for at least the first year as severe hearing loss may appear during this time. Any ongoing concerns about hearing warrant ongoing surveillance into school age.

5. TREATMENT

Thyroxine treatment is started as soon as the diagnosis has been confirmed by thyroid function tests (preferably the same day as the evaluation). There remains some controversy regarding the initial starting dose of thyroxine and how quickly the TSH should be normalised. (see section 8.1). A recommended starting dose is approximately 10 micrograms/kg/day; however a lower starting dose of 6-8 micrograms /kg/day in Australian children has been associated with normal long term intellectual outcome⁵. Dosage needs to be adjusted at follow-up visits with the aim of keeping the free T4 concentration at the upper end of the normal range and the TSH level suppressed into the normal range. TSH may take several months to suppress after treatment is started, particularly with low dose regimens.

Serum free thyroxine concentration may increase significantly following an oral dose of thyroxine⁶. Therefore blood for thyroid function tests should preferably be taken immediately before a dose is due.

Thyroxine should be given by crushing the required tablet dose with a little milk or water, using a teaspoon or syringe. It should never be added to a bottle of formula. Prepared suspensions may lead to unreliable dosage³. The dosage should be repeated if the baby vomits or regurgitates immediately afterwards.



5.1 Common Dosages

Dosage varies with body size and must be adjusted for the individual. As a guide, common doses are:

0-6 months	25-50 µg/day	8-15 µg/kg/day
6-12 months	50-75 µg/day	7-10 µg/kg/day
1-5 years	5-100 µg/day	7.5-7 µg/kg/day
5-10 years	100-150 µg/day	3-5 µg/kg/day
>10-12 years	100-200 µg/day	2-4 µg/kg/day

After infancy, dosages are kept commonly in the region of 100 µg/m²/day.

6. COUNSELLING

Parents with babies with congenital hypothyroidism are naturally very apprehensive about the future. They need to be reassured about the favourable prognosis, and the likelihood that their child will grow into a normal, healthy adult with normal intelligence. In those cases due to thyroid dysgenesis, the parents should be told that the condition is very unlikely to recur in subsequent children. However, with permanent thyroid dyshormonogenesis, there is likely to be autosomal recessive inheritance, with a 1:4 risk of recurrence. There are a number of pamphlets or booklets available, which give useful information to parents concerning congenital hypothyroidism.

7. FOLLOW-UP

7.1 Objectives

The object of therapy is to ensure normal growth and development. Thyroid function tests are repeated at each visit with a view to maintaining the free thyroxine concentration in the upper normal range and the TSH within the normal range.

7.2 Frequency

The baby is re-examined and repeat thyroid tests are performed at two weeks after starting therapy, at six weeks, at three months and two to three monthly for the first year of life. More frequent review may be necessary if problems arise. Thereafter, clinical examination and thyroid function testing occurs three monthly unless there has been a significant dose change, a change to or from soy-based formula⁶ or there is a clinical indication. Reviews can be done at about four monthly intervals after the age of three years and in older children four to six monthly.

7.3 Hearing Tests

In patients with suspected dyshormonogenesis, hearing tests should be performed regularly for at least the first year of life (see Section 4.3.6).



7.4 Bone Age Xrays

There is no need to check bone age Xrays if growth patterns are normal.

7.5 Developmental Assessment

This may be indicated clinically or to allay parental anxiety. Despite early treatment, some evidence suggests that children with congenital hypothyroidism, particularly those with severe hypothyroidism, may have a lower IQ or, more commonly, exhibit slight psychomotor abnormalities such as problems with balance skills, fine motor tasks, learning difficulties and behavioural problems associated with normal IQ. This may apply particularly to children with severe CH at birth (athyrotic, low FT4, delayed bone age)⁷.

7.6 Transient Hypothyroidism

If there is any question of the congenital hypothyroidism being transient in nature, the child can safely be given a trial off therapy at the age three years⁸. In cases where this is strongly suspected e.g. where there is a history of maternal thyroid disease and thyroid receptor antibodies are present, this can be tried earlier by slow reduction of dose or allowing the child to "grow out" of its dose. The baby must be very carefully monitored during this period and TFTs followed closely.

7.7 Compliance

The importance of treatment compliance in determining outcome has to be stressed to the parents. Outside the neonatal period, poor compliance may be suggested by a high TSH and a FT4 which is normal or high. This occurs when medication has been given regularly for the few days leading up to the blood test, but erratically over the previous weeks to months.

8. ADDITIONAL NOTES

8.1 Initial Dosage of Thyroxine.

Controversy regarding the initial starting dose of thyroxine centres around whether a more rapid normalisation of the thyroid function tests (in particular the suppression of TSH into the normal range) with the use of higher starting doses improves the long-term developmental outcome. Although early studies demonstrated no significant difference between controls and children with congenital hypothyroidism⁹, other studies later suggested that outcome may not be as good in infants with severe hypothyroidism^{10,11}. However, the New England Congenital Hypothyroidism Collaborative have reported completely normal IQ scores and school attainment up to the age of 9 years¹². These results have been taken to indicate that the effects of prenatal hypothyroidism can be completely reversed by early treatment and it has been suggested that the normal outcome in the New England study may be related to the use of a higher dose of thyroxine. This is supported by studies in Quebec¹³ and in Norway¹⁴, although not in England¹⁵. Data from the South Australian cohort, which provides the only long term followup data in Australia, in which low dose thyroxine has been used for 22 years with normal intellectual outcome, does not support this contention⁵. The American Academy of Pediatrics recommends a starting dose of 10-15 µg/kg/day, particularly in severe hypothyroidism, with very frequent monitoring of TFTs (1-2 monthly) during the first year. The Academy recommends that the free T4 level should be within the upper half of the normal range within 2 weeks of starting therapy and the TSH < 20 mU/L within the first month³. Vogiatzi and Kirkland emphasised that children treated



initially with 50 µg/day soon required a reduction to either 37.5 or 25 µg/day and that these infants required more frequent monitoring during the first 2 months to avoid iatrogenic hyperthyroidism¹⁶.

8.2 Persistently High TSH Concentrations

This may reflect a resetting of the pituitary-thyroid feedback threshold by in utero hypothyroidism¹⁷ or perhaps be a more sensitive indicator of CNS hypothyroidism than FT4 levels and hence of inadequate thyroxine replacement¹⁸. The use of high doses of thyroxine to suppress TSH quickly may sometimes lead to FT4 levels well above the normal range. While some of these babies are clinically euthyroid, others may exhibit signs of toxicity and very disturbed sleep patterns, excessive crying etc.

8.3 Overtreatment with Thyroxine

This may cause craniosynostosis, accelerated growth and maturation, disturbed sleep patterns, altered tempo of brain maturation and effects on temperament¹⁹. Rovet has shown more behaviour problems (social withdrawal, hyperactivity, conduct problems and anxiety) in children treated with initial starting doses of thyroxine >10µg/kg/day²⁰. Therefore it seems prudent to use thyroxine doses ranging between 8-12 µg/kg/day in most babies with CH. In those with very severe CH at birth initial doses up to 15 µg/kg/day can be considered with careful monitoring for

REFERENCES

1. Francis I. Newborn screening in Australia and New Zealand 1984 - 1990. *Med J Aust* 1991; 821 - 3.
2. Burrow G N, Fisher D A, Larsen P R. Maternal and fetal thyroid function. *New Engl J Med* 1994; 331: 1072 - 8.
3. American Academy of Pediatrics Newborn Screening for Congenital Hypothyroidism: Recommended guidelines. *Pediatrics* 1993; 91: 1203 - 8.
4. Grant D B, Smith I, Fuggle P W, Tokar S, Chapple J. Congenital hypothyroidism detected by neonatal screening: relationship between biochemical severity and early clinical features. *Arch Dis Child* 1992; 67: 87 - 90.
5. Fletcher J M, Coxon R, Penfold J, Ranieri E, Gerace R, Woodroffe P, Robertson E. Normal intellectual outcome after low dose thyroxine replacement for congenital hypothyroidism. International symposium on Therapeutic Outcome of Endocrine Disorders: Efficacy, Innovation and Quality of Life. November 13-16 1997, Palm Beach Gardens, USA.
6. Deam D R, Campbell D G, Ratnaik S. Effect of oral intake of thyroxine on results of thyroid function tests in patients receiving thyroid replacement therapy. *Med J Aust* 1983; 2: 374 - 6.
7. Jabbar M A, Larrea J, Shaw R A. Abnormal thyroid function tests in infants with congenital hypothyroidism: the influence of soy-based formula. *J Amer Coll Nutr* 1997; 16: 280 - 2.
8. Murphy G, Hulse J A, Jackson D, Tyrer P, Glossop J, Smith I, Grant D. Early treated hypothyroidism: development at 3 years. *Arch Dis Child* 1986; 61: 761 - 5.
9. Davy T, Daneman D, Walfish P G, Ehrlich R M. Congenital hypothyroidism: effect of stopping treatment at 3 years of age. *Am J Dis Child* 1985; 139: 1028 - 30.
10. New England Congenital Hypothyroidism Collaborative. Characteristics of infantile hypothyroidism discovered on neonatal screening. *J Pediatr* 1984; 104: 539 - 44.
11. Glorieux J, Dussault J H, Morissette J et al. Follow up at ages 5 and 7 on mental development in children with hypothyroidism detected by Quebec screening program. *J Pediatr* 1985; 107: 913 - 5.
12. Rovet J, Ehrlich R, Sorbara D. Intellectual outcome in children with fetal hypothyroidism. *J Pediatr* 1987; 110: 700 - 4.



13. New England Congenital Hypothyroidism Collaborative. Elementary school performance of children with congenital hypothyroidism. *J Pediatr* 1990; 116: 27 - 32.
14. Dubois J-M, Richer F, Glorieux J, Deai C, Dussault JH. Should all patients with congenital hypothyroidism be treated with 10 - 15 ug.kg/day levothyroxine? *Pediatr Res* 1994; 35: 98A.
15. Heyerdahl S, Kase B F, Lie S O, Intellectual development in children with congenital hypothyroidism in relation to recommended thyroxine treatment. *J Pediatr* 1991; 118: 850 - 7.
16. Tillotson S L, Fuggle P W, Smith I, Ades A E, Grant D B. Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. *Br Med J* 1994; 440 - 5.
17. Vogiatzi M G, Kirkland. Frequency and Necessity of Thyroid Function Tests in Neonates and Infants with Congenital Hypothyroidism. *Pediatrics* 100; 3:6.
18. Germak J A, Foley T P Jr. Longitudinal assessment of L-thyroxine therapy for congenital hypothyroidism. *J Pediatr* 1990; 117: 211 - 9.
19. Heyerdahl S, Kase B F. Significance of elevated serum thyrotropin during treatment of congenital hypothyroidism. *Acta Paediatr* 1995; 84: 634 - 8.
20. Rovet J F, Ehrlich R M, Sorbara D-L. Effect of thyroid hormone level on temperament in infants with congenital hypothyroidism detected by screening of neonates. *J Pediatr* 1989; 114: 63 - 8.
21. Rovet J F, Ehrlich R M. Long-term effects of L-thyroxine therapy for congenital hypothyroidism. *J Pediatr* 1995; 126: 380 - 6.