

Congenital Hypothyroidism An Update

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- 2 weeks after the first screening test
- preterm birth <37 week's</p>
- Iow birth weight< 2000g</p>
- very low-birth weight
- Large WT>4500g
- Gestational age>40 weeks
- Admission to NICU
- Non thyroidal illness
- Curr Opin Endocrinol Diabetes Obes 2020

- Syndromes
- Malformations
- use of steroid during pregnancy
- specimen collection within the first 24 hours of life
- Multiple births

- Maternal thyroid disease is considered a risk factor for a delayed TSH rise, hence requiring a second screening between days 15 and 30 of life
- Suggest testing TGAb, TPOAb, and TSH receptor antibodies

- TSH values at the first screening ranging 6.5-9.9 mU/L
- Maternal diabetes
- Maternal treatment with amiodarone
- Maternal/neonatal iodine exposure
- Congenital heart disease
- Dopamin administration
- Steriod administration
- Transfusion

Screening of neonates of mother with ATD

 Newborn whose mother is receiving an antithyroid drug. T4 and TSH values return to normal within 1 to 3 weeks



Screening of neonate with Down syndrome

- Two week
- Two month
- Every 6-12 months till 3 years old

What's the mechanism of hypothyroidism in down syndrome?

• Extra chromosome 21 results in genomic dosage imbalance of dosage-sensitive genes interfering with thyroid hormone production

Screening of Neonate with Hemangioma

Thyroid testing is required monthly until one year of age

Normal variation of T4& FT4

Before 4 wk of age

- T4= 10.7 ± 1.4ug/dl
- FT4= 2.03± 0.3 ng/dl
- After four weeks of life
- T4=7-16 ug/dl
- FT4= 0.8-2.3 ng/dl
- One to four weeks
- TSH= 1-6

Up to date 2021

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Concentrations of free T4, T4, T3, and TSH in preterm and term infants, in cord blood at birth and at 7, 14, and 28 days of age (mean \pm 1 SD)

Gestation (weeks)	Age of specimen	Free T4 (ng/dL)	T4 (microgram/dL)	T3 (ng/dL)	TSH (mU/L)
23-27 weeks	Cord	1.28 ± 0.4	5.4 ± 2.0	20 ± 15	6.8 ± 2.9
	7 d	1.47 ± 0.6	4.0 ± 1.8	33 ± 20	3.5 ± 2.6
	14 d	1.45 ± 0.5	4.7 ± 2.6	41 ± 25	3.9 ± 2.7
	28 d	1.50 ± 0.4	6.1 ± 2.3	63 ± 27	3.8 ± 4.7
28-30 weeks	Cord	1.45 ± 0.4	6.3 ± 2.0	29 ± 21	7.0 ± 3.7
	7 d	1.82 ± 0.7	6.3 ± 2.1	56 ± 24	3.6 ± 2.5
	14 d	1.65 ± 0.4	6.6 ± 2.3	72 ± 28	4.9 ± 11.2
	28 d	1.71 ± 0.4	7.5 ± 2.3	87 ± 31	3.6 ± 2.5
31-34 weeks	Cord	1.49 ± 0.3	7.6 ± 2.3	35 ± 23	7.9 ± 5.2
	7 d	2.14 ± 0.6	9.4 ± 3.4	92 ± 36	3.6 ± 4.8
	14 d	1.98 ± 0.4	9.1 ± 3.6	110 ± 41	3.8 ± 9.3
	28 d	1.88 ± 0.5	8.9 ± 3.0	120 ± 40	3.5 ± 3.4
≥37 weeks	Cord	1.41 ± 0.3	9.2 ± 1.9	60 ± 35	6.7 ± 4.8
	7 d	2.70 ± 0.6	12.7 ± 2.9	148 ± 50	2.6 ± 1.8
	14 d	2.03 ± 0.3	10.7 ± 1.4	167 ± 31	2.5 ± 2.0
	28 d	1.65 ± 0.3	9.7 ± 2.2	176 ± 32	1.8 ± 0.9

Adapted with permission from: Williams FL, Simpson J, Delahunty C, et al. Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. J Clin Endocrinol Metab 2004; 89:5314.



When T4 is abnormal?

low T₄ defined as 2 SDs< mean

J Pediatr Endocrinol Metab. 2012

Low T4 &Normal TSH

- Anticonvulsants
- preterm infants
- NTI
- TBG deficiency
- Central hypothyroid
- Birth asphyxia
- Dopamine
- High-dose glucocorticoids

low T4 &Low or normal TSH

Central hypothyroidism

- Transient hypothyroxinemia of prematurity
- Nonthyroidal illness
- primary hypothyroidism with delay TSH elevation

Low T4 & Normal TSH

What should we do?

Recheck,TSH,FT4 or T3Ru for TBG deficiency

Low T4 & Delayed TSH elevation

- Primary hypothyroidism and delayed TSH elevation ,common in infants who are preterm, LBW, or acutely ill
- SGA <10th was an independent risk factor for delayed TSH rise
- All screening should be retested at 2 &4 weeks
- Up to date 2020

Delayed TSH elevation

- Full-term, normal-birth weight infants who require admission to a NICU have acute illness that may result in delayed TSH rise
- In term infants four factors associated with delayed TSH rise
- PDA
- Administration of vancomycin
- insulin
- Furosemide

Curr Opin Endocrinol Diabetes Obes 2020 -

When the test is abnormal?

• TSH>10 mU/lite FreeT4<0.8ng/dl

At two weeks ,We should think to CH

J Clin Endocrinol Metab,2011 AAP 2006 Uptodate 2016 Orphanet Journal of Rare Diseases 2010

When TSH is abnormal?

Before 2 wk of age TSH >20 mIU/L
After 2 wk of age TSH >10 mIU/L
indicative of primary CH

Indian J Pediatr 2018

Confirmatory Serum Thyroid Test

TSH ≥20 mU/L

T4 <8 μg/dL

FreeT4<0.8ng/dl

Considered as hypothyroid

J Clin Endocrinol Metab,2011

Korean J Pediatr 2015

Horm Res Paediatr 2014

Subclinical hypothyroidism

• TSH>9mU/lit FT4=0.8 -2.3ng/dl

J Clin Endocrinol Metab, 2011

Secondary hypothyroidism

• TSH<9mU/lit N ,↓ TSH

• T4<5-7ug/dl

• FT4<0.8ng/dl

↓ T4

 \downarrow FT4

• J Clin Endocrinol Metab, 2011

TBG deficiency

- TSH<9mU/lit
- T4<5ug/dl

↓ T4

• FT4=0.8 -2.3ng/dl

Normal FT4

Normal TSH

• T3 Ru = 24% to 37%

个T3 Ru

J Clin Endocrinol Metab, 2011

Severity of CH

- The severity of CH was biologically assessed as serum FT4 ng/dL
- Severe <0.4
- Moderate
- Mild

0.4 to <0.8 0.8 to 1.16

Mild hypothyroidism

- Serum TSH 5 to 20 mU/L
- With a borderline low or normal range FT4

- If the initial serum TSH is >20 mU/liter
- irrespective of the serum free FT4
- immediately Second sampleAfter that
- we recommend starting thyroid hormone treatment as soon as possible
 - J Clin Endocrinol Metab, 2011
- Up to date 2021

Normal T4 &Elevated TSH

If TSH 10-20mIU/L

for two times with a normal serum FT4 value

J Clin Endocrinol Metab, 2011

Horm Res Paediatr 2014

low T4 &Elevated TSH TSH 10-20mIU/L

Normal T4 &Elevated TSH

• If the serum TSH has not normalized by

4 -6 wk of age

persistant hyperthyrotropinemia>10 we recommend treating

- J Clin Endocrinol Metab, 2011
- The Journal of Maternal-Fetal & Neonatal Medicine 2018
- Up to date 2021

T4 <3ug/dl 2 SDs< mean
Low FT4 <0.8 ng/dL 2 SDs< mean

At 3,6 week

- irrespective of TSH should be treated with levothyroxine
- Then reevaluation off therapy should be planned after 3 y of age
- The Journal of Maternal-Fetal & Neonatal Medicine 2018

lf increase Trend of TSH TSH = 6 mIU/l TSH = 9mIU/l

Guideline of treatment in term and premature neonates.

TSH $>$ 20 10mIU/L with any	Treatment should be started in premature and
level of FT4	term neonates.
>10 TSH <20 10mIU/L with	Treatment should be started in premature and
low FT4	term neonates.
>10 TSH <20 10mIU/L and	TSH should be rechecked after two weeks in
normal FT4	premature and term neonates. If it was still
	TSH was above 10mIU/L , treatment should be
	started. In premature infants, if TSH was less
	than 10mIU/L, it should be rechecked six and
	ten weeks later.
6 < TSH < 10 10 mHU/L and low	In premature peopates (The FT4 and TSH
ETA	should be rechecked after two weeks. If it still
1 14	had the same result treatment should be
	started as suspected central hypothyroidism
	Clinicians should evaluate the pituitary axis
	especially the adrenal axis but whenever TSH
	was above10mIII/L treatment should be
	started with suspicious to primary
	hypothyroidism)
	In term neonates (if free T4 was low in 3-
	6weekswith normal TSH without any reason)
	again treatment should be started)

Guideline of treatment in term and premature neonates

Normal FT4 and TSH in premature neonates	TSH and FT4 should be rechecked at six and ten weeks
6 <tsh 10miu="" <10="" and<br="" l="">normal FT4</tsh>	Premature and term patients should be referred to pediatric endocrinologists, and treatment should be started based on the clinical symptoms and ultrasound by an endocrinologist. In the lack ofaccess to a pediatric endocrinologist,free t4 and TSH should be measured until reaching the normal range.The increasing trend of TSH needs treatment as well.
TSH <6 10 mIU/L with normal T4 or free T4	Follow-up should be done in premature and term neonates. If free t4 was low, treatment should be started based on suspicion of central hypothyroidism.
Persistent TSH >10 10mIU/L at six weeks of age	Treatment

Dose oflevothyroxine inprimary and central hypothyroidism based on FT4

FT4 (ng/d L)	Dose of levothyroxine in primary hypothyroidism	Dose of levothyroxine in central hypothyroidism
< 0.4 ng /dl	10-15 µg/kg	10-15 µg/kg
0.4 - 0.8 ng/dl	10 µg/kg	5-10 μg/kg
>0,8 ng/dl	5-10 μg/kg	No treatment

1 mg/dL = 0.07770008 pmol/L

Mild hypothyroidism

A form of compensated CH in which there is a mild increase in TSH (6–20 mU/l) with normal

FT4

It may be transient or permanent

Horm Res Paediatr 2014
What do you do?

- If TSH 6 -20 mU/l with normal FT4
- Retesting 1-2 weeks later

Persistent TSH >10miU/L at 4- 6 week

What do you do?

 we suggest diagnostic imaging
 If a small/ectopic thyroid gland is seen should treatment

HormRes Paediatr 2014

J. Child Health 2015

What do you do?

- If the thyroid gland is normal
- Repeat TFT every two weeks till TSH normalizes

• Or

- Discussion with the family
- starting L-T 4
- Retesting off treatment

Infants with minor abnormalities in thyroid function

- TSH= 6 to 10 mIU/L
- free T4 = normal
- it is not clear whether thyroid hormone treatment is indicated
- In such an infant, imaging is helpful
- Dysgenesis
- Normal or high uptake values in normally located

Infants with minor abnormalities in thyroid function

- If there is abnormal imaging
- Treatment should be started
- Otherwise it should be follow up

Treatment

Levothyroxin dose should be adjusted according to the infant's

- Clinical response
- FT4
- TSH
- FT4, rather than the total T4, has to be measured periodically to assess the concentration of the biologically relevant unbound or free form of circulating T4

What is our ultimate goal?

To Ensure Normal Growth & Development 0.5 to 5.0 mU/L TSH optimally 0.5-2mIU/L 1.4 to 2.3 ng/dl Free T4 10 to 16 mcg/dL**T**4 During the first 3 years of life

- PEDIATRIC RESEARCH 2009
- Orphanet Journal of Rare Diseases 2010
- AAP2006
- Uptodate 2020

Failure of Treatment

Preparation of L-thyroxin Is Not Appropriately Active

Absorption of L-thyroxin Is Incomplete

Child Is Not Receiving The Medication

Drug exposure to high temperature

Failure of Treatment

- Iarge hemangiomas with high deiodinase activity
- Malabsorption
- increased degradation (anticonvulsants)

Failure of Treatment

- Soy Formulas (within an hour)
- Ferrous Sulfate
- > Aluminum Hydroxide
- Bile Acid Sequestrants
- Calcium
- colic" drops (<u>simethicone</u>)
- Up to date 2021

Risk of overtreatment

- Prolonged overtreatment (>3 months) should be avoided
- Persistently high fT4> 2.4 ng/dL or T4 >16 mcg/dL with suppressed TSH <0.5 mU/L may adversely effect
- Tempo of brain development
- Cognitive development
- Temperament
- Attention span

premature craniosynostosis.

Treatment with special care

 In newborn with cardiac insufficiency, starting L-T4 dose should be at 50 % of the target replacement dose and should be further increased in accordance with fT4 levels after 2 weeks

Curr Opin Endocrinol Diabetes Obes 2020

infant with CH & Rehabilitation Care

- Sick neonates with CH in intensive care units, unable to receive medication via enteral route, or those under NPO status during pre or postoperative care will require IV L-T4 therapy
- with IV dose generally 50% to 75% of the oral dose

Curr Opin Endocrinol Diabetes Obes 2020 –

Biotin supplementation

- Biotin supplementation is the treatment in biotinidase deficiency but can causing falsely low levels of TSH and elevated FT4
- patient with biotinidase deficiency had erroneous thyroid function testing that was suggestive of hyperthyroidism.
- Once biotin supplementation was withheld, a true diagnosis of CH was possible

Monitoring of dose

Monitoring of dose

- Two weeks after the initiation of <u>levothyroxine</u> treatment and every 2 weeks until serum TSH level is normalized.
- Every one to three months between one and three years of age.
- Every 6 to 12 months thereafter until growth is complete

- Serum FT4 and TSH should be determined at least 4 6 h after the last dose
- Reduction of L-T 4 dose should not be based on a single increase in FT4 during treatment
- Lab evaluations should be carried out 4–6 weeks
 after any change in L-T 4 dose

Horm Res Paediatr 2014

Increase FT4& suppressed TSH

- Decreasing L-T 4 by 30% for 2–3 weeks
- Rechecking thyroid function
- If TSH \geq 10 mU/l is demonstrated

CH is confirmed

- Otherwise the dose can be reduced further
- with retesting after another 4 weeks

Horm Res Paediatr 2014

This results may be explained by

- Several missed doses all at once just before a scheduled blood draw
- Mild underdosing
- Thyroid hormone resistance

- several missed doses of levothyroxine just before scheduled blood test monitoring.
- If this history is obtained from the parents, no dose increase in indicated
- But we would recommend rechecking thyroid function tests in one month.
- Up to date 2021

- If no history of missed doses
- A small increase levothyroxine dose with a recheck of fT4 and TSH in four weeks
- As the TSH normalizes
- if the patient remains clinically euthyroid, this supports mild undertreatment

- With a small increase in levothyroxine dose
- if any thyrotoxic clinical features develop, this supports thyroid hormone resistance
- we should return to the previous, lower levothyroxine dose

Thyroid hormone resistance

 In this situation, if the levothyroxine dose is increased to normalize TSH, patients may manifest thyrotoxic clinical features

Transient mild Thyroid hormone resistance

- Some infants with CH manifest persistent mild TSH 5 to 20 mU/L despite serum fT4 or T4 in the target range
- This infants suffering of transient mild thyroid hormone resistance, because of intrauterine hypothyroidism producing a resetting of the pituitary-thyroid feedback threshold with relative pituitary resistance

Transient mild Thyroid hormone resistance

- Thyroid hormone resistance improves with age but can persist
- More common in infants <one year of age</p>
- In such cases, if the levothyroxine dose is increased to lower TSH into the normal range, the infants may manifest clinical features of overtreatment.
- Thus, in these cases, we recommend using serum fT4 or T4 as the primary test to adjust levothyroxine dosing not TSH

Anti convulsion drug and thyroid function test

 Change the dose of the drug base on thyroid function test

Central hypothyroidism

- Micropenis
- Undescended testes
- Features of diabetes insipidus
- Hearing loss
- Nystagmus
- Cleft lip/cleft palate
- Optic nerve hypoplasia/septo-optic dysplasia
 Up to date 2021

Diagnostic evaluation

Thyroid Radionuclide Uptake

We do **not** recommend routinely because the results do not alter management **Can be done with TSH>50 miu/l** Can Be done Within The First Week After Starting Treatment Should Never Be Delayed To Obtain Scan

Associated congenital malformations

young adults

- Ieft ventricular diastolic dysfunction
- impaired exercise capacity
- increased intima-media thicknesss
- Obesity
- Up to date 2021

Associated congenital malformations

- CHD fourfold higher than control
- ASD, VSD, PS
- Hearing problem
- Kidney disease polycystic kidney odds ratio 13.2
- GI Alagille syndrome type 1

• <u>The Journal of Pediatrics</u>2008

Hearing Problems

- They have some hearing impairment as young adults three times the rate in the general population
- Hearing loss was seen more frequently in patients with athyreosis and a gland in situ (Pendred syndrome) but not in patients with an ectopic gland.
- More severe disease associated with hearing loss
- Up to date 2021

Hearing Problems

- Sensorineural hearing loss as well as conductive deficits in young adults with CH
- Hearing loss in CH is mostly bilateral, mild to moderate, and in some cases requires hearing aids
- Up to date 2021

Hearing Problems

- We recommend routine hearing tests in infants with congenital hypothyroidism
- Up to date 2021

Neurodevelopmenal outcome

Depends on

- Adequacy of treatment
- Severity of CH at diagnosis
- Etiology
- Delayed bone maturation at diagnosis
- Later time of thyroid function normalization
- Poor compliance to treatment
- Socio demographic factors
- Dose initiation <5 mcg/kg/day</p>
- Up to date 2021

Later time of thyroid function normalization

- Infants who achieved normal thyroid function within two weeks after therapy had
- Better cognitive, attention, and achievement scores compared with those who took longer than two weeks to normalize their thyroid function
Early versus delayed treatment

 If Treatment Is Delayed after 2 weeks
A 20 Point Deficit In Both Mental And Psychomotor Development Is Observed

infants who started "early" (12 to 30 days of age) had IQ scores 15.7 points higher than infants who started "later" (>30 days of age

Neurodevelopmental outcome

During The First Year Of Life, Infants With ▶T4 <10 mcg/dl ▶Accompanied By TSH > 15 Mu/L

Have Lower IQ Values Than infants

AAP2006

Severe hypothyroidism & Neurocognitive outcomes

Infant With

- Initial T4 Level < 5 µg/dl</p>
- Delay Skeletal Maturation at Birth.

May have Permanent Intellectual Sequelae

Higher mean serum T4 levels at diagnosis were associated with higher verbal IQ scores and arithmetic skills

Early versus delayed treatment

 ✓ Psychometric testing at 30 months and again at six years of age showed that patients started on treatment at the earlier age < 13 days and on the higher dose ≥ 9.5 mcg/kg/day had better scores than patients started at a later age and lower dose of levothyroxine

✓ Up to date 2021

High versus low starting dose

High versus low starting dose

- Recommended starting dose of 10 to 15 mcg/kg/day have a better IQ outcome than <10 mcg/kg
- IQ was 6–9 points lower when levothyroxine dose less than 10 mcg/kg/day
- No difference in IQ when initial doses above 10 mcg/kg/day
- Up to date 2021

High versus low starting dose

High L-T4 starting doses

- FT4 normalizes in 3 days.
- TSH returns to the target range by 2 weeks of therapy.
- Result in the attainment of normal global IQ at 4 years of age and young adults
- Growth and bone age maturation are not affected by such a high dose
- Recommended for severely affected patients
- Early and high-dose treatment resulted in visual perception and motor coordination

with 12–17 µg/kg levothyroxin

Up to date 2021

High versus low starting dose

- A high initial L-T4 dose can normalize serum T4 in 3 days and TSH by two weeks of therapy.
- The majority of full-term infants with severe CH require a short-term high dose L-T4 (50 ug per day) with dose reduction to 37.5 ug per day after TSH is normalized to avoid over treating.
- > Up to date 2021

PROGNOSIS

- **Neurodevelopment and functional outcomes**
- is generally good for infants who are treated early
- Beginning at two to six weeks of life
- > Optimally through the first three years of life
- Their global IQs are similar to those of normal infants

PROGNOSIS

- inadequately treated in the first three years of life
- Ievothyroxine dose <5 mcg/kg/day had worse cognitive outcomes
- TSH >15 mU/L
- T4 <6.6 mcg/dL during treatment</p>
- Initial T4<2 mcg/dL</p>
- immature skeletal

At 3 Years Of Age

Discontinue Treatment And Retest Serum T4/TSH After 4 Weeks especially

If the serum TSH value has not increased

Infant is normal

Almost 100% Of Children With True CH Have Elevated TSH Levels After 4 Weeks Off Of Treatment.

AAP2006

At 3 Years Of Age

4 weeks After discontinued the drug

- TSH> 10 means True CH
- Should be treated again

At 3 Years Of Age

 Serum TSH levels above 10.0 mU/L on at least 2 occasions

or

 if sTSH was above 20.0 mU/L in a single blood collection

- Cases in which serum TSH values ranged between 5.0 and 9.9 mU/L with normal FT4 were considered indicative of persistent hyperthyrotropinemia ,not requiring the reintroductionof treatment
- Needs follow up

- Transient CH was diagnosed if serumTSH was below 5.0 mU/L with normal FT4 at least in two occasions
- Patients with initial HT that subsequently showed serum TSH below 5.0 mU/L on at least 3 consecutive blood collections were classified as affected by transient CH

 During treatment if Serum TSH> 10 mU/L after the first year of life

- AAP1993
- Up to date 2021

if

> initial thyroid scan shows ectopic

Confirmed by ultrasonographic examination

 If the results of thyroid function tests are inconclusive, careful follow-up and subsequent retesting are indication

- Maternal ATD , TSH tend to return to normal within 1–3 weeks after birth without treatment
- Large hepatic hemangiomas increased type 3 deiodinase, resulting in "consumptive hypothyroidism"
- The hypothyroidism resolved by 16 months of age as the hemangioendothelioma regressed
- Up to date 2021

- **Excessive iodine exposure to the fetus or newborn**
- Recover within a few weeks of discontinuing the iodine
- Such cases require monitoring of TSH and fT4 to confirm recovery to euthyroidism but generally do not need treatment
- Up to date 2021

Drugs

- Steroids & dopamine causing transient central hypothyroidism with low FT4 and a low or normal TSH level
- Carbamazepine and sodium valproate can cause transient mild hypothyroidism
- Aminophylline and caffeine in preterm infants
- Up to date 2021

 Transient mild elevation of TSH above the normal reference value for age is observed in the first month of life in infants born from mothers affected by autoimmune thyroiditis
Up to date 2021

Maternal autoimmune thyroiditis

Transplacental Passage of Maternal TSH Receptor Blocking Antibodies

- Transient CH
- Scintigraphy show no uptake despite the presence of a eutopic thyroid gland
- Positive TRBAb.
- Hypothyroidism last up to 3–6 months after birth as maternal antibody levels fall.
- In some cases, should start therapy
- planning a reevaluation of therapy at a later time
- Maternal blocking antibodieshis, cleared one to six months
- Up to date 2021

Only recommend TRBAb determinations in a case where

- A previous child has had transient CH and mother has a diagnosed autoimmune thyroid disease and is pregnant again
- Up to date 2021

- if initial imaging by ultrasound showed a eutopic normal-sized thyroid gland
- if the infant has never had an abnormal TSH elevation while on levothyroxine
- Never required an increase in dose
- Requires a relatively low dose to maintain euthyroidism <2.5 mcg/kg/day
- Up to date 2021

Neurocognitive assessment

Evaluation of

- intersubjectivity and interaction skills at 12, 18, and 24 months
- language and fine motor development at 36 months
- intellectual ability and requirements for reading and writing at 5years
- Specific learning abilities, attention at 7 years

References

- Thyroid disease in children
- Up to date 2021
- Curr Opin Endocrinol Diabetes Obes 2020
- Update on congenital hypothyroidism

