

بِسْمِ اللَّهِ النُّورِ





Congenital Hypothyroidism

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Congenital Hypothyroidism



- Because newborns are asymptomatic at birth, screening programs developed worldwide
- One of the commonest *treatable* causes of mental retardation

congenital hypothyroidism

- 1:4,000 newborns
- inverse relationship between age at diagnosis and IQ
- Most newborn with CH no clinical manifestations of thyroid deficiency
- Diagnosis is based on newborn screening programs by heel-stick

Etiology

- 85 percent sporadic
- 15 percent hereditary

Major Causes of Congenital Hypothyroidism and their Approximate Frequency

Cause	Frequency
Thyroid dysgenesis – ectopia, aplasia, or hypoplasia	1:4500
Inborn errors of thyroxine synthesis (dysmorphogeneses)	1:30,000
Maternal antibody-mediated hypothyroidism	1:25,000-1:100,000
Central hypothyroidism	1:25,000-1:100,000
Transient hypothyroidism	
Europe – iodine deficiency	1:100
North America – autoimmune thyroiditis; iodide excess	1:50,000
Thyroxine-binding globulin deficiency – causes low serum T4 concentrations but not hypothyroidism	1:4300

Thyroid dysgenesis

- Agenesis
- Hypoplasia
- Ectopy ⇔ Two-thirds

Most cases sporadic
Some cases familial/genetic

Dyshormonogeneses

Autosomal recessive

- iodide transport
- Thyroid peroxidase
- Production of abnormal thyroglobulin
- Iodotyrosine deiodinase deficiency

Defect in thyroid peroxidase impaired
iodide oxidation and organification

Central hypothyroidism

Associated with

- Septo-optic dysplasia
- Cleft lip
- Cleft palate
- Birth trauma
- Asphyxia

Central hypothyroidism

- Other pituitary hormone deficiencies
- Hypoglycemia or micropenis

Clinical Manifestations

- Within 1 month of birth %5-%10
- Within 2 month of birth %30
- Within 12 month of birth %70
- Birth length and weight are normal
- head circumference may be increased. The absence of knee epiphyses occur in males than females (40 versus 28 percent
- Occasionally lethargy, slow movement

Clinical Manifestations

- Hoarse cry
- Feeding problems
- constipation
- macroglossia
- umbilical hernia
- Large fontanel, hypotonia
- Dry skin
- Hypothermia
- Prolonged jaundice

Newborn Screening Programs

- Blood is collected onto filter paper cards after heel prick
- Three to five days after delivery
- Some programs obtain a second specimen between two and six weeks

Diagnostic Studies

At recall

- Infant should be examined
- Blood sample for confirm hypothyroidism

Confirmation Diagnosis

Normal Values For TSH

After the first four weeks

• 0.5 to 6 mU/L

Adult range at about two years of age

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 ± 1 SD)

gestation (weeks)	Age of infant	Free T ₄ (ng/dL)	T ₄ (microgram/dL)	T ₃ (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

Low T₄ & Elevated TSH

- **TSH > 10 mU/lite** **FreeT₄ < 0.7 ng/dl**

At two weeks ,We should think to CH

J Clin Endocrinol Metab, 2011

TSH > 10 mU/lite

AAP 2006

Normal T₄ & Elevated TSH

■ **TSH > 10 mU/lit**

fT₄ = 0.8 - 2.3 ng/dl

Subclinical hypothyroidism

J Clin Endocrinol Metab, 2011

When TSH is abnormal?

- Before 2 wk of age TSH > 20
- After 2 wk of age TSH > 10

indicative of primary CH

Confirmatory Serum Thyroid Test

TSH ≥ 20 mU/L

T₄ < 8 μ g/dL

FreeT₄ < 0.7 ng/dl

Considered as hypothyroid

J Clin Endocrinol Metab, 2011

Korean J Pediatr 2014

Horm Res Paediatr 2014

Secondary Hypothyroidism

- TSH < 9 mU/lit fT₄ < 0.7 ng/dl
- T₄ < 5 ug/dl

Secondary hypothyroidism

- J Clin Endocrinol Metab, 2011

Normal T₄ & Elevated TSH

- Down syndrome
- Hyperthyrotropinemia persists until 18
years of age or later.

Persistent Elevated TSH

- Persistent \uparrow TSH > 10 mIU/L
- Should be treated

AAP 2006

TBG deficiency

- **TSH** < 9 mU/lit **fT₄** = 0.78-2.3 ng/dl
- **T₄** < 5 ug/dl
- **T₃ Ru** 24% to 37% > 45%

J Clin Endocrinol Metab, 2011

low T₄ & nor or low TSH

- Central hypothyroidism.
- Premature infants
- Non thyroidal illness
- ↓ Thyroxin-binding globulin (TBG)
- Birth asphyxia
- Anticonvulsants
- High-dose glucocorticoids

Except central hypothyroidism

- Treatment of these infants may do more harm than good

A low T_4 and normal TSH

seen in $\Delta\%$ of neonates

Request a second blood sample for measurement

- TSH
- T_4 resin uptake
- Free T_4

primary TSH and VLBW

- An average age for TSH rise is २.० days (< 1500 g)
 - All VLBW infants should be rescreened at २, ६, and 10 weeks of age
 - Or
 - until they weigh more than 1500 g.
- Or Recheck at २ weeks

Thyroid radionuclide uptake

Not recommend routinely
in infants with TSH > 40 $\mu\text{u/l}$ are useful

Thyroid Radionuclide Uptake

It Should Be done Within

The First Week After Starting
Treatment

Treatment Should Never Be Delayed
To Obtain Scan

Clinical Management

- Education of parents
- Etiology of CH
- lack of correlation of parental lifestyle during pregnancy with causes of the disease
- Benefit of early diagnosis
- Appropriate manner in which TH is administered
- Importance of adherence to the treatment plan
- Importance of periodic follow-up care

Treatment

- **Treatment should begin as soon as possible, preferably within the first two weeks of life**

Goal Of Treatment

To Ensure Normal Growth & Development
Within 1- 2 Weeks of Starting Therapy

- TSH 0.15-2 MIU/L
- Free T₄ 1.4 to 2.3 ng/dl

- Up to date 2018
- PEDIATRIC RESEARCH 2009
- Orphanet Journal of Rare Diseases 2010

Who Should Be Treated

Normal T₄ & Elevated TSH

- If the serum TSH (> 10 mIU/L) has not normalized by 4-6 weeks of age

we recommend treating

- J Clin Endocrinol Metab, 2011
- Up to date 2018

Who Should Be Treated

- If the initial TSH is greater than 2.5 **mU/liter**
- we also recommend starting thyroid hormone treatment with any T_4 level

- J Clin Endocrinol Metab, 2011

- Up to date 2018

Who Should Be Treated

if serum TSH is elevated $10-20$ mU/liter
with normal FT₄

- Recheck a serum TSH and free T₄ in 1-2 wk.

we recommend treating

- If the serum TSH has not normalized >10 mIU/L

- Up to date 2018

Who Should Be Treated

- TSH is, ≥ 10 mIU/L
- repeating a serum TSH and free T_4 in one week
- Some neonates will normalize
- if the serum TSH does not normalize by four to six weeks of age with low T_4
- we recommend starting thyroid hormone treatment. As secondary hypothyroidism

Treatment

AAP recommends levothyroxine

8-12 ug/kg in most babies

Infants with very low T₄ (<5 ug/dL) or FT₄ <
0.7 ng/dL

should receive 12.5 to 15 mcg/kg/day

Treatment

Levothyroxin dose should be adjusted according to the infant's

- Clinical response
- TSH
- FT₄
- T₄

Treatment

- **Thyroxin tablets can be crushed daily, mixed with a few milliliters of water, breast milk, or formula**

Treatment

- A failure of the T_4 to increase into the upper half of the normal range by **4 weeks** after initiation of l-thyroxin administration
- should serve to alert the physician that the child may
 - TBG deficiency
 - preparation of l-thyroxin is not appropriately active
 - absorption of l-thyroxin is incomplete
 - child is not receiving the medication

Lab evaluation

- should be determined at least 4 h after the last L-T 4 administration

Failure of treatment

- FT₄ to increase into the upper half of the reference range(**2 ng/dL**) by 2 weeks
- and/or**
- TSH to decrease to less than 2.0 mU/L within 2 weeks after initiation of L-T₄

- J Clin Endocrinol Metab, 2012

Failure of treatment

**Should alert the physician that the child
may not be receiving adequate L-T₄**

J Clin Endocrinol Metab, 2012

Interfere With The Absorption

- Soy Formulas (within an hour)
- Ferrous Sulfate
- Aluminum Hydroxide
- Bile Acid Sequestrants
- Calcium
- infant "colic" drops (simethicone)

Premature

- Currently the evidence base does not indicate cognitive benefit from thyroid therapy of hypothyroxinemia of prematurity in the absence of TSH elevation.

- AAP²⁰⁰⁶

Monitoring

Recheck T₄, TSH

- 2 to 4 weeks after initial treatment is begun
- Every 1 to 2 months in the first 6 months
- Every 3 to 4 months between 6 months and 3 years of age
- Every 6 to 12 months from 3 years of age to end of growth

AAP 2006

Monitoring

- At More Frequent Intervals When Compliance Is Questioned Or Abnormal Values Are Obtained
- **Lab Test Should Be Performed 2 - 4 Weeks After Any Change In Thyroxin Dosage**

FOLLOW-UP

Routine clinical examination, including

- **Assessment of growth and development, at regular intervals**
- **Approximately every few months during the first 3 years of life**
- **Infants with CH have risk for other congenital anomalies, which occur in 10% of these infants as compared to 3% in the general population**

▪

FOLLOW-UP

- CHD
- Hearing Screening
- visual processing problems
- speech delay

prognosis

**During The First Year Of Life,
Infants With**

- **T₄ < 1.0 Ug/dl**
- **Accompanied By TSH > 15 Mu/L**

**Have Lower IQ Values Than infants
Whose T₄ Levels Were Held
Constant At Higher Concentrations**

AAP 2006

prognosis

An optimal cognitive outcome depends on both

- Adequacy of treatment
- Timing of postnatal therapy particularly in severe cases of CH ($T_4 < 5$ ug/dL)

Prognosis

Infant With

- Initial T₄ Level < 5 μg/Dl
- Delay Skeletal Maturation At Birth.

Have Permanent Intellectual Sequelae

Prognosis

During treatment

- four or more episodes TSH (>5 mU/L) after the age of 6 months associated with school delay

AAP 2006

Normal Psychomotor

- Severe CH Can Achieve Normal Psychomotor Development At 10 To 30 Months
- If Treatment Is Initiated Before 13 Days of Age And An Initial Dose of $> 9/5 \mu\text{g}/\text{Kg}/\text{Day}$ Is Used
- If Treatment **Is Delayed or A Lower Dose Is Used**, A **20 Point** Deficit In Both Mental And Psychomotor Development Is Observed

Assessing permanence of CH

At 3 Years Of Age

- Serum TSH levels **above 10.7 mU/L** on **at least 2 occasions**
- or
- if sTSH was **above 20.7 mU/L** in **a single blood collection**

Assessing permanence of CH

- 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 reintroduction of treatment
- Needs follow up

Assessing permanence of CH

- **Transient CH** was diagnosed if serum TSH was below $5/10$ mU/L with normal FT₄ **at least in two occasions**
- Patients with initial HT that subsequently showed **serum TSH below $5/10$ mU/L on at least 3 consecutive blood collections** were classified as affected by transient CH

Assessing permanence of CH

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

- AAP 1993
- Up to date 2021

Assessing permanence of CH

if

- initial thyroid scan shows **ectopic**
- Confirmed by ultrasonographic examination

Assessing permanence of CH

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

Transient hypothyroidism

- Maternal ATD , TSH tend to return to normal within 1–3 weeks after birth without treatment

■ Up to date ۲۰۲۱

Transient hypothyroidism

- Large **hepatic hemangiomas** increased type Ⅲ deiodinase, resulting in "consumptive hypothyroidism"
- The hypothyroidism **resolved by 16 months of age** as the hemangioendothelioma regressed

• Up to date 2021

Assessing permanence of CH

if

- initial thyroid scan shows ectopic/absent gland confirmed by ultrasonographic examination

Transient conditions

- Postnatal iodine exposure is 2-3 times more common among premature
- Newborn whose mother is receiving an antithyroid drug. T₄ and TSH values return to normal within 1 to 3 weeks
- it is impossible to determine whether the hypothyroidism is permanent or transient.

Overtreatment

FT₄ above 2/4 ng/dL more than 3 weeks

- Craniosynostosis
- Disturbed sleep
- Behavior problem
- Hyperactivity
- Cognitive development
- Attention deficit

نوزاد مبتلا به سندرم دان در چه زمان هائی
باید آزمایش تیروئید در این ها انجام شود

➤ اسکرین

➤ دو هفتهگی

➤ دو ماهگی

➤ هر ۶-۱۲ ماه تا سه سالگی

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 ± SD)

Thyroid hormones neonates - Clinical Practice Guideline: Eur

Secure | https://www.uptodate.com/contents/image?imageKey=PEDS%2F72215&topicKey=PEDS%2F5840&search=thyroid%20function%20tes...

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رستگار

