Neonatal
पाठशाला

National Neonatology Forum
Gujarat State Chapter

Seminar

09/02/2022, Wednesday | **03:30 pm - 04:30 pm**

Congenital Hypothyroidism - A Pandora's Box

Dr Sandip Trivedi
President, NNF Gujarat

Dr Prashant Kariya
Hon. Secretary, NNF Gujarat

Dr Ashish Mehta
Advisor

Dr Somashekhar Nimbalkar
Advisor

Dr Yogesh Parikh
Project Incharge

Dr Nehal Patel
Chairperson

Dr Zalak Shah
Expert

Dr Shalmi Mehta
Expert

Dr Khushboo Mehta
Presenter

National Neonatology Forum

Gujarat State Chapter

CONGENITAL HYPOTHYROIDISM

A Pandora's box

Presenter: Dr. Khushboo Mehta

Embryogenesis

- The thyroid gland is the first endocrine organ to develop in the fetus.
- By 12 weeks of gestation, the thyroid gland is capable of synthesis and secretion of thyroxine (T4) and tri-iodothyronine (T3), but the activity of the hypothalamic-pituitary-thyroid axis remains low till 18 to 20 weeks of gestation.
- The placenta regulates the passage of maternal thyroid hormones to the fetus. This transfer of T4 is essential, especially in the first trimester, when the fetal thyroid axis has yet to mature.

- Thus a hypothyroid fetus in a euthyroid mother has some neuroprotection and near normal cognitive outcomes.
- But a hypothyroid fetus in a hypothyroid mother has the most substantial deficits.

Congenital Hypothyroidism

- Congenital hypothyroidism is a common cause of preventable mental retardation.
- Its worldwide incidence is 1:3000-4000 live births, while the incidence is higher in India, 1:1000 live births. (as per ISPAE 2018)
- The prevalence differs with sex, ethnicity and birthweight.
- There is increased risk in infants who are low birth weight infants, those with congenital heart disease, other congenital malformations, and Down's syndrome.

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ZHONGGUO DANG DAI ER KE ZA ZHI
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Chinese. doi: 10.7499/j.issn.1008-8830.2011121

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PMID: 34020742

Language: Chinese | English

Risk factors for neonatal congenital hypothyroidism: a Meta analysis

张 骥 (Ji ZHANG)* and 李 杨 (Yang LI)*,*

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Results A total of 20 studies were included, with 13 case-control studies and 7 cross-sectional studies. There were 11 564 neonates in total, with 3 579 neonates in the case group and 7 985 neonates in the control group. The Meta analysis showed that advanced maternal age (*OR*=2.111, 95%*CI*: 1.275-3.493), thyroid disease during pregnancy (*OR*=3.365, 95%*CI*: 1.743-6.500), gestational diabetes mellitus (*OR*=2.158, 95%*CI*: 1.545-3.015), anxiety (*OR*=3.375, 95%*CI*: 2.133-5.340), medication during pregnancy (*OR*=2.774, 95%*CI*: 1.344-5.725), radiation exposure during pregnancy (*OR*=3.262, 95%*CI*: 1.950-5.455), family history of thyroid disease (*OR*=8.706, 95%*CI*: 5.991-12.653), low birth weight (*OR*=2.674, 95%*CI*: 1.895-3.772), fetal macrosomia (*OR*=1.657, 95%*CI*: 1.187-2.315), preterm birth (*OR*=2.567, 95%*CI*: 2.070-3.183), post-term birth (*OR*=2.083, 95%*CI*: 1.404-3.091), twin pregnancy or multiple birth (*OR*=3.455, 95%*CI*: 1.958-6.096), and birth defects (*OR*=6.038, 95%*CI*: 3.827-9.525) were risk factors for CH in neonates. **Conclusions** Advanced maternal age, gestational thyroid disease, gestational diabetes mellitus, anxiety, medication during pregnancy, radiation exposure during pregnancy, family history of thyroid disease, low birth weight, fetal macrosomia, preterm birth, post-term birth, twin pregnancy or multiple pregnancy, and birth defects may increase the risk of CH in neonates. **[Chin J Contemp Pediatr, 2021, 23(5): 505-512]**

Key words: Congenital hypothyroidism; Risk factor; Meta analysis; Neonate

Causes

- Transient hypothyroidism
- Maternal antithyroid medication
- TSH receptor blocking antibodies
- Hypothyroxinemia of prematurity
- Iodine deficiency
- Iodine excess
- TBG excess
- Liver haemangioma

Causes

- Permanent hypothyroidism
  - Thyroid dysgenesis (aplasia, hypoplasia or ectopia)- Most common (85%)
  - Dyshormonogenesis (10-15%)
  - TSH resistance (less common)
  - Central hypothyroidism

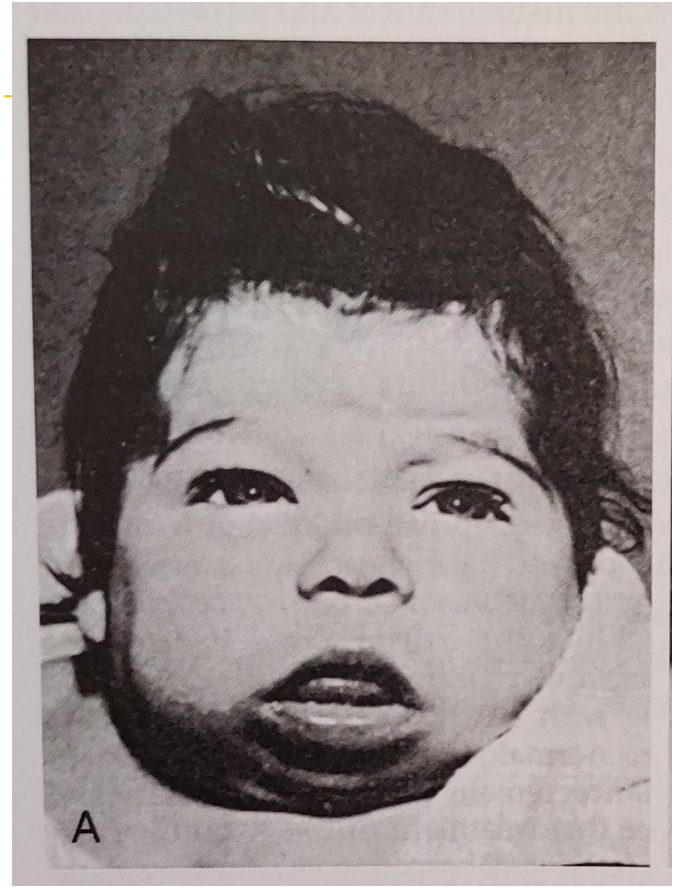
- Hypothyroxinemia with delayed TSH elevation (atypical CH)

Clinical manifestations

- Hypothyroidism should be considered in any infant with prolonged jaundice, transient hypothermia, enlarged posterior fontanel, failure to feed properly or respiratory distress during feeding.
- The classic signs evolve during the first few weeks after birth.
- There is delay in bone maturation with rapid reduction in growth rate after birth, with progressively worsening myxedema.
- Additional signs include muscular hypotonia, hyporeflexia, anaemia, constipation, umbilical hernia, hoarseness of voice.
- Generally these babies are quiet and well-behaved.

- However, it is notable that over 95% newborns with CH are asymptomatic at birth.
- 10% present with diagnostic features in 1st month;
- 35% in first 3 months;
- 70% by 1st year

- This emphasizes on the need of universal newborn screening for early diagnosis and treatment.



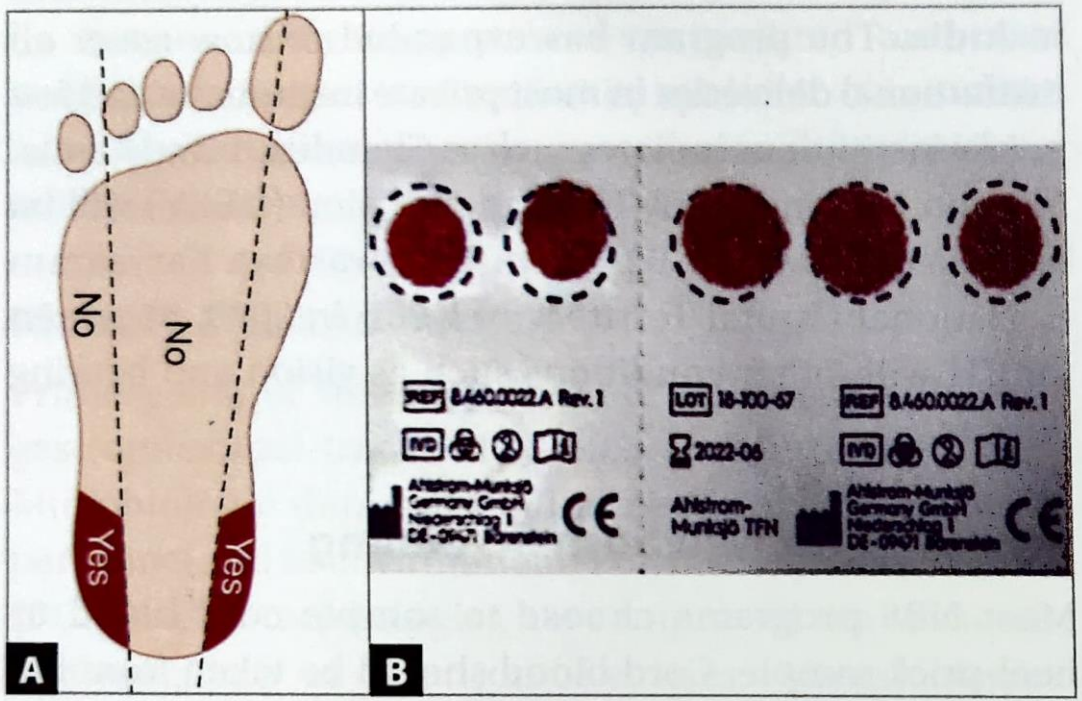
- The typical facies are characterised by a depressed nasal bridge, narrow forehead, puffy eyelids, protruding tongue

Screening

- Either cord blood or postnatal sample at 48-72 hours is collected for screening.
- Approaches to screen:

1. Primary TSH, backup T4- it is the most effective method to diagnose primary CH, but likely to miss central hypothyroidism, TBG deficiency and hypothyroxinemia with delayed elevation of TSH.
2. Primary T4, backup TSH- likely to miss milder/subclinical cases in which T4 is initially normal.
3. Concomitant T4 and TSH- ideal approach, but incurs higher costs.

- A second screening may be required in: preterm neonates, LBW and VLBW neonates, ill neonates admitted in NICU, specimen collection done in the first 24 hours of life, multiple births especially same sex twins.
- The repeat specimen is collected at 2 weeks of age or 2 weeks after the first screening test.



Figs. 1A and B: Newborn screening. (A) Correct site for heel prick sample; (B) Dried blood spot on filter paper.
Image Courtesy: Dr Seema Kapoor, Maulana Azad Medical College, New Delhi.

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REVIEW ARTICLE

Newborn Screening Guidelines for Congenital Hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) – Part I: Screening and Confirmation of Diagnosis

M. P. Desai[1] · R. Sharma[2] · I. Riaz[3] · S. Sudhanshu[4] · R. Parikh[1] · V. Bhatia[4]

Received: 5 August 2017 / Accepted: 13 December 2017

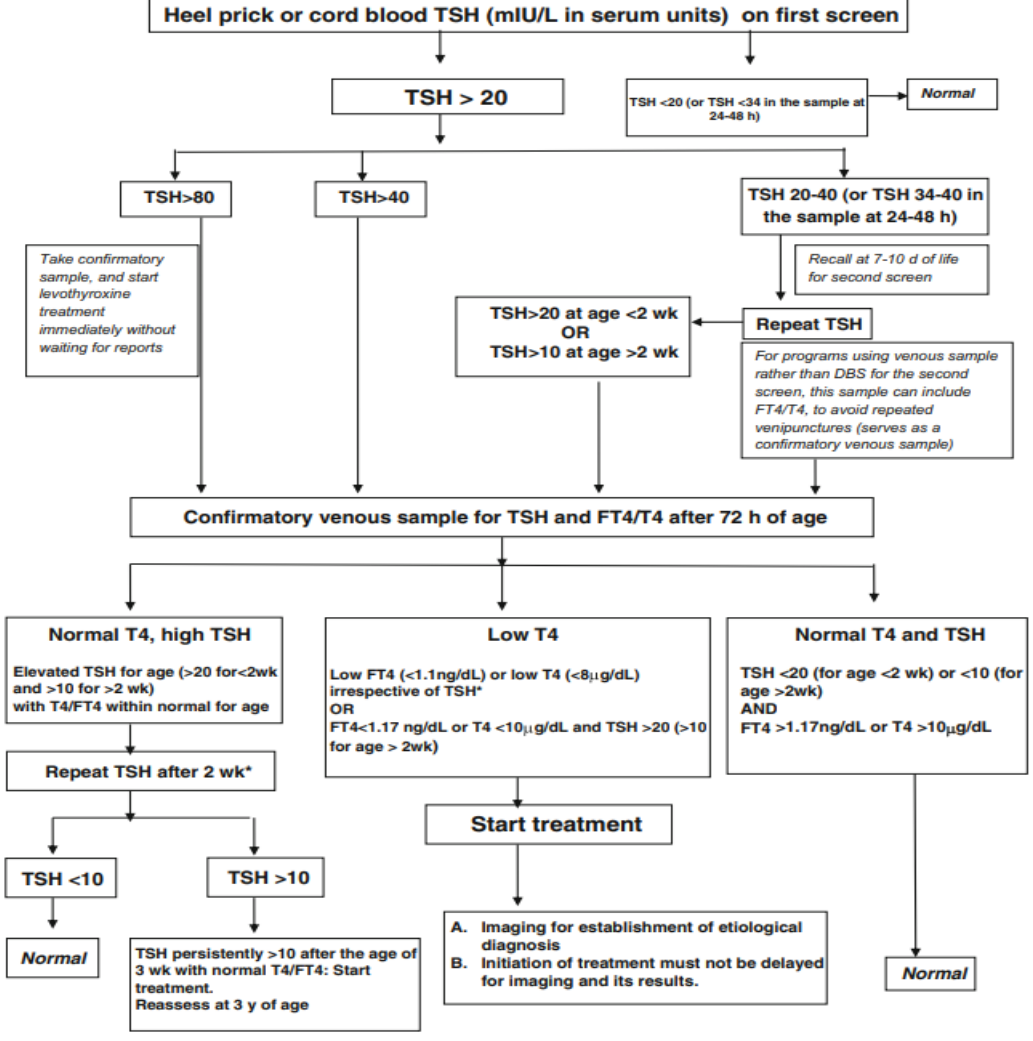
The Indian Journal of Pediatrics
https://doi.org/10.1007/s12098-017-2576-x

REVIEW ARTICLE

Newborn Screening Guidelines for Congenital Hypothyroidism in India: Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) – Part II: Imaging, Treatment and Follow-up

S. Sudhanshu[1] · I. Riaz[2] · R. Sharma[3] · M. P. Desai[4] · R. Parikh[4] · V. Bhatia[1]

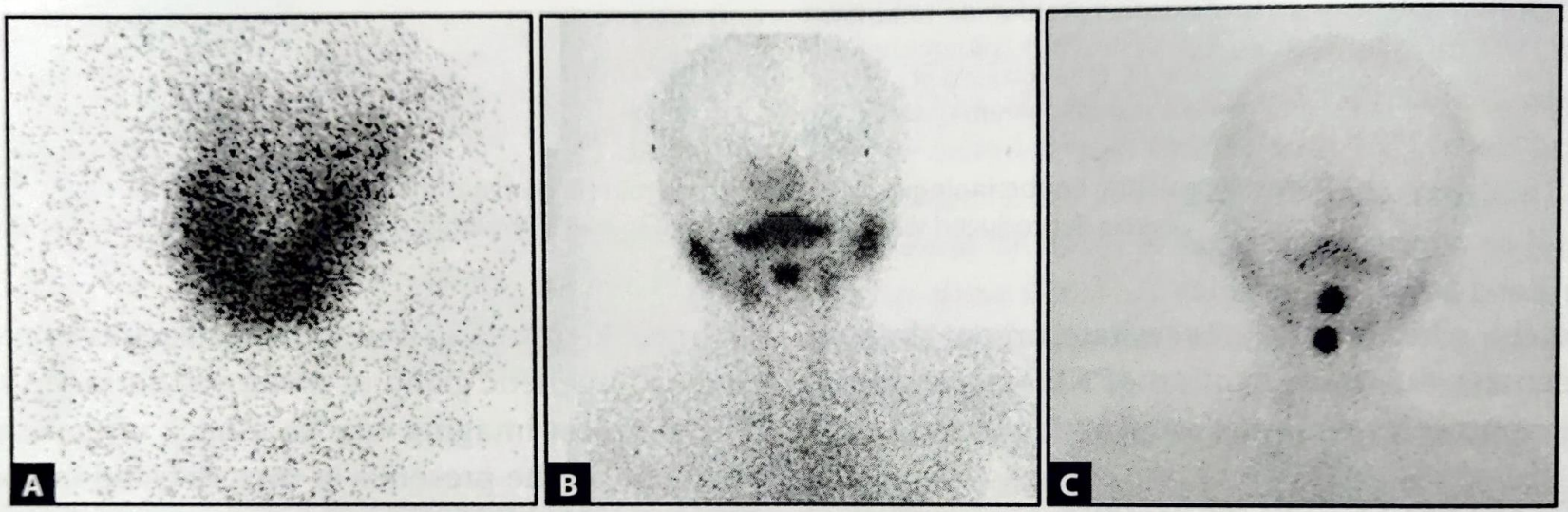
Received: 5 August 2017 / Accepted: 13 December 2017


Heel prick or cord blood TSH (mIU/L in serum units) on first screen
TSH > 20
TSH <20 (or TSH <34 in the sample at 24-48 h)
Normal
TSH>80
TSH>40
TSH 20-40 (or TSH 34-40 in the sample at 24-48 h)
Take confirmatory sample, and start levothyroxine treatment immediately without waiting for reports
Recall at 7-10 d of life for second screen
TSH>20 at age <2 wk OR TSH>10 at age >2 wk
Repeat TSH
For programs using venous sample rather than DBS for the second screen, this sample can include FT4/T4, to avoid repeated venipunctures (serves as a confirmatory venous sample)
Confirmatory venous sample for TSH and FT4/T4 after 72 h of age
Normal T4, high TSH
Elevated TSH for age (>20 for<2wk and >10 for >2 wk) with T4/FT4 within normal for age
Low T4
Low FT4 (<1.1ng/dL) or low T4 (<8μg/dL) irrespective of TSH*
OR
FT4<1.17 ng/dL or T4 <10μg/dL and TSH >20 (>10 for age > 2wk)
Normal T4 and TSH
TSH <20 (for age <2 wk) or <10 (for age >2wk)
AND
FT4 >1.17ng/dL or T4 >10μg/dL
Repeat TSH after 2 wk*
Start treatment
TSH <10
TSH >10
Normal
TSH persistently >10 after the age of 3 wk with normal T4/FT4: Start treatment.
Reassess at 3 y of age
A. Imaging for establishment of etiological diagnosis
B. Initiation of treatment must not be delayed for imaging and its results.
Normal
*Consult pediatric endocrinologist; rule out TBG (thyroid binding globulin) deficiency

Imaging

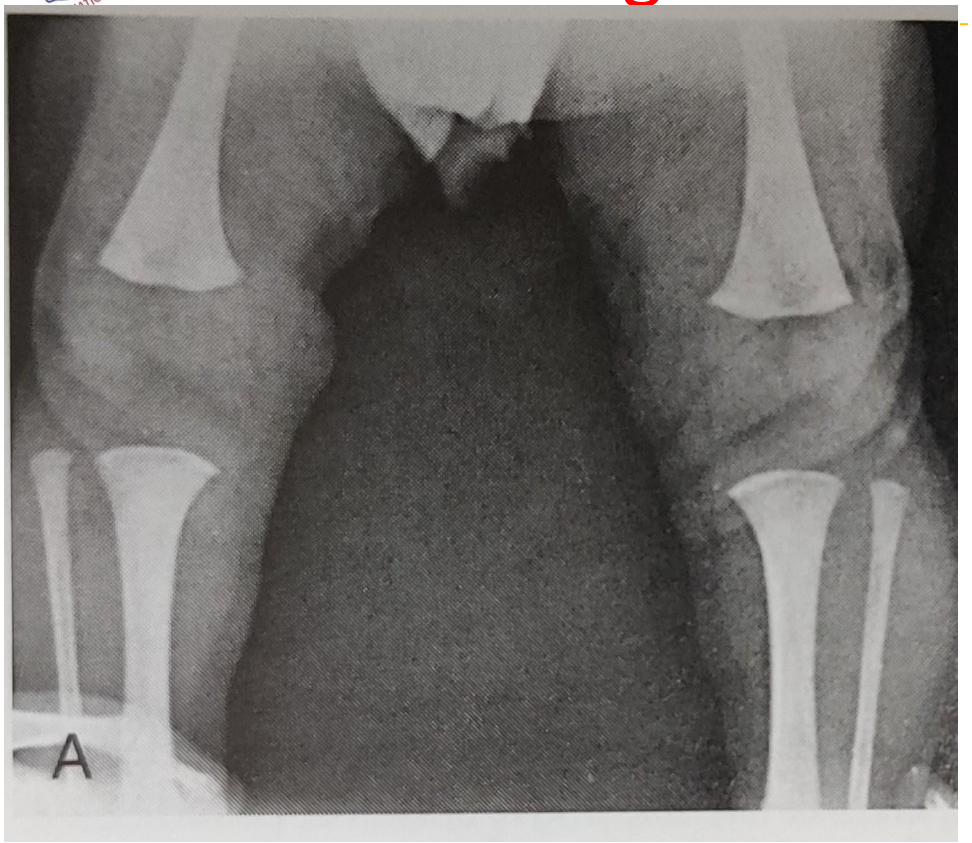
- Imaging (ultrasound and scintigraphy) should be done once CH is biochemically confirmed.
- Both modalities complement each other and hence wherever feasible, both should be perfomed.
- However, treatment should not be delayed in waiting for nuclear scan.
- If nuclear scan is unavailable, an ultrasound can be performed, which will differentiate thyroid aplasia and hypoplasia from other causes of CH.
- But, an ultrasound may miss ectopic thyroid gland.

- If scintigraphy could not be performed within 7 days of starting thyroxine therapy, it should be deferred until child is 3 years old, when thyroid replacement can be discontinued for a period of 6 weeks, and scan performed thereafter.



Figs. 2A to C: Images of thyroid scan suggesting: (A) Dyshormogenesis; (B) Lingual thyroid gland; (C) Dual ectopic gland.
Image Courtsey: Dr Aashima Dabas.
Source: Institute of Nuclear Medicine and Allied Sciences.

Other Investigations



- Radiograph of knee for skeletal maturation may be helpful in assessing the severity and duration of intrauterine hypothyroidism.

- Investigations may be needed to rule out other congenital malformations, especially congenital heart diseases, and renal disorders.
- Universal hearing screening and regular hearing assessment should also be done.

Treatment

Table 2 Criteria on venous confirmatory sample results for initiation of levothyroxine therapy in term newborns

1. Low T4 (<100 nmol/L or 8 μg/dL) or low FT4 (<12 pmol/L or <1.1 ng/dL) irrespective of TSH.
2. Mild low T4 (<128 nmol/L or 10 μg/dL) or low FT4 (<15 pmol/L or 1.17 ng/dL) in the presence of elevated venous TSH >20 mIU/L if age is <2 wk and >10 mIU/L if age is >2 wk.
3. Normal T4/FT4 with persistently elevated TSH >10 mIU/L at age > 3 wk.

*from ISPAE, 2018

Treatment

- Treatment with L-thyroxine should be started as soon as possible, no later than first 2 weeks of life.
- The initial dose is 10-15µg/kg/day.
- The tablets should be crushed and fed directly or mixed in small amount of water or breast milk.
- Ferrous sulphate, calcium supplements, soya and fibre interfere with its absorption and should be administered at least 2 hours apart.

- The goal of treatment is to normalize T4 level at the earliest.
- T4 should be kept in upper half of normal range (10-16µg/dl) or free T4 1.4-2.3 ng/dl, with the TSH suppressed in normal range.

Monitoring and follow-up

- T4 and TSH levels are monitored as per the following schedule -
- 0-6 months:
- FT4 testing is done at first follow-up at 2 weeks after the initiation of treatment, at which time we expect normalization of T4.
- 4 weeks after that, T4 and TSH are tested, at which time normalization of TSH is expected.
- After that, TSH and T4 testing is done every 2 monthly till 6 months of age.

- 6 months to 3 years: every 3 months
- Beyond 3 years: every 3-6 months, till growth and pubertal development is completed.
- Any dose change needs to be followed up by a biochemical evaluation after 4 to 6 weeks.
- Regular growth and development monitoring should be done by plotting on appropriate growth charts.

- After 3 years of treatment, a repeat TFT should be done after stopping medication for 6 weeks in babies who were started treatment without complete evaluation, in preterm sick neonates, with USG showing normal thyroid gland or mild dyshormonogenesis.

Congenital hypothyroidism: recent advances

Ari J. Wassner and Rosalind S. Brown

Purpose of review
This review summarizes significant recent advances in the epidemiology, pathophysiology, and treatment of congenital hypothyroidism.

Recent findings
The apparent incidence of congenital hypothyroidism has more than doubled in recent years because of several factors, including more inclusive diagnostic criteria, shifting demographics, and increasing survival of preterm infants. The greatest increase has occurred in mildly affected patients, many of whom have a eutopic thyroid gland. Congenital hypothyroidism may be transient or persistent, but the natural history cannot be predicted by severity at diagnosis. In premature infants, who are especially vulnerable to hypothyroidism, the rise in thyroid-stimulating hormone may be delayed and therefore detected only by routine follow-up screening. Recent studies of defects in thyroid hormone synthesis have focused on the role of mutations in the dual oxidase system and of a novel apical iodide transporter, anoctamin 1. Finally, emerging data suggest that exposure to excess thyroid hormone may be as harmful as hypothyroidism to long-term cognitive development.

Summary
Although newborn screening has virtually eradicated mental retardation due to congenital hypothyroidism in parts of the world, new information continues to accumulate and new questions to arise about the diagnosis, physiology, and optimal management of this disorder.

Keywords
congenital hypothyroidism, eutopic, prematurity, preterm, thyroid

Outcome

- Neurodevelopmental outcome can be excellent in infants who had prompt diagnosis and treatment, especially when treatment is started by 2 weeks of life.
- Subtle defects in visuospatial processing, selective memory, sensorimotor functions may be noted in infants having severe CH.
- In those whose diagnosis was delayed, severe cognitive and behavioral defects are noted, depending on the severity of CH.

- More than 80% of infants given replacement therapy before 3 months of age have an IQ of >85 but may show signs of minimal brain damage, including impairment of arithmetic ability, speech, or fine motor coordination in later life. When treatment is started between 3-6 months, the mean IQ is 71 and when delayed to beyond 6 months, the mean IQ drops to 54.

(*Congenital Hypothyroidism Consensus Conference Group. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism-2014)

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Volume 31, Number 3, 2021
Mary Ann Liebert, Inc.
American Thyroid Association
DOI: 10.1089/thy.2020.0333

Congenital Hypothyroidism: A 2020–2021 Consensus Guidelines Update— An ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology

Paul van Trotsenburg,[1,*] Athanasia Stoupa,[2–5,*] Juliane Léger,[6,7] Tilman Rohrer,[8] Catherine Peters,[9] Laura Fugazzola,[10,11] Alessandra Cassio,[12] Claudine Heinrichs,[13] Veronique Beauloye,[14] Joachim Pohlenz,[15] Patrice Rodien,[16] Regis Coutant,[17] Gabor Szinnai,[18] Philip Murray,[19,20] Beate Bartés,[21] Dominique Luton,[22,23] Mariacarolina Salerno,[24] Luisa de Sanctis,[25] Mariacristina Vigone,[26] Heiko Krude,[27] Luca Persani,[28,29] and Michel Polak[2–5,30–32]

Evidence. In the vast majority of early and adequately treated children with CH, neurodevelopmental and school outcomes level are normal (90,91,159–161), and intellectual disability—defined as an IQ <70—has virtually disappeared (162). In the past, patients with severe CH treated with a low initial LT4 dose had lower IQ scores (although within normal range), and subtle neurological deficits in cognitive and motor development (163,164) when compared with control

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Pediatric Quality of Life in Congenital Hypothyroidism: an Indonesian Study

Nur Rochmah, Muhammad Faizi, Carrina Dewanti and Ahmad Suryawan

Department of Child Health, Dr. Soetomo General Hospital, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

Background and Objectives: Thyroxine is important for brain development. Improper hypothyroid treatment may lead to cognitive and motor impairment, thereby affecting the quality of life. We analyzed the correlation between age at first treatment, length of treatment, initial levothyroxine (LT4) dose, and serum levels of free thyroxine (fT4) and thyroid stimulating hormone (TSH) and pediatric quality of life in patients with congenital hypothyroidism (CH). **Materials and Methods:** This research was a cross-sectional study of 41 children with CH who consumed LT4 for at least 3 months during March 2019-December 2019. The quality of life was assessed from parents' reports using the Pediatric Quality of Life Inventory (PedsQL) generic scale. Spearman correlation analysis was carried out, and statistical significance was set at $p<0.05$. **Results:** A total of 17 of the 41 children were girls. The mean PedsQL scores in physical and psychosocial functioning were 78.12 (68.75-100) and 233.30 (215-251.67), respectively. Age at first treatment was correlated with physical functioning ($r=-0.501$, $p<0.05$) and psychosocial functioning ($r=-0.440$, $p<0.05$). The initial LT4 dose was negatively correlated with physical functioning ($r=-0.568$, $p<0.05$) and psychosocial functioning ($r=-0.482$, $p<0.05$). The length of treatment showed a positive correlation with physical functioning ($r=0.776$, $p<0.05$) and psychosocial functioning ($r=-0.852$, $p<0.05$). However, the serum fT4 and TSH levels were not correlated with quality of life in children with CH ($p>0.05$). **Conclusion:** Age at first treatment, initial dose of LT4, and length of treatment were correlated with quality of life in children with CH.

Key Words: Congenital hypothyroidism, Child, Quality of life, PedsQL

THANK YOU