MIXEDEMUL CONGENITAL : CUM SA-L RECUNOASTEM SI CUM SA-L TRATAM?

CRISTINA PREDA

Universitatea de Medicina si Farmacie
“Grigore T. Popa”, Iasi

MOST COMMON PREVENTABLE CAUSES OF MENTAL RETARDATION

TERMINOLOGIE
mixedem-hipotiroidie congenitala

- **MIXEDEM PRIMAR**
- **MIXEDEM SECUNDAR (hipotiroidie centrala)**
- **HIPOTIROIDISM PERIFERIC (defect de transport, metabolism sau actiune)**
- **HIPOTIROIDIE PERMANENTA**
- **HIPOTIROIDIE TRANZITORIE**
- **HIPOTIROIDIE SINDROMICA**

1.	**Primary hypothyroidism**
	Thyroid dysgenesis: hypothyroidism due to a developmental anomaly
	(Thyroid ectopia, athyreosis, hypoplasia, hemiagenesis)
	Associated mutations: (these account for only 2% of thyroid dysgenesis cases; 98% unknown)
	TTF-2,
	NKX2.1,
	NKX2.5
	PAX-9
	Thyroid dyshormonogenesis: hypothyroidism due to impaired hormone production
	Associated mutations:
	Sodium-iodide symporter defect
	Thyroid peroxidase defects
	Hydrogen peroxide generation defects (DUOX2, DUOXA2 gene mutations)
	Pendrin defect (Pendred syndrome)
	Thyroglobulin defect
	Iodotyrosine deiodinase defect (DEHAL1, SECISBP2 gene mutations)
	Resistance to TSH binding or signaling
	Associated mutations:
	TSH receptor defect
	G-protein mutation: pseudohypoparathyroidism type 1a
2.	**Central hypothyroidism (syn: Secondary hypothyroidism)**
	Isolated TSH deficiency (TSH β subunit gene mutation)
	Thyrotropin-releasing hormone deficiency
	Isolated, pituitary stalk interruption syndrome (PSIS), hypothalamic lesion, e.g. hamartoma
	Thyrotropin-releasing hormone resistance
	TRH receptor gene mutation
	Hypothyroidism due to deficient transcription factors involved in pituitary development or function
	HESX1, LHX3, LHX4, PIT1, PROP1 gene mutations
3.	**Peripheral hypothyroidism**
	Resistance to thyroid hormone
	Thyroid receptor β mutation
	Abnormalities of thyroid hormone transport
	Allan-Herndon-Dudley syndrome (monocarboxylase transporter 8 [MCT8] gene mutation)
4.	**Syndromic hypothyroidism**
	Pendred syndrome - (hypothyroidism- deafness - goiter) **Pendrin mutation**
	Bamforth-Lazarus syndrome - (hypothyroidism - cleft palate - spiky hair) **TTF-2 mutation**
	Ectodermal dysplasia - (hypohidrotic - hypothyroidism - ciliary dyskinesia)
	Hypothyroidism - (dysmorphism - postaxial polydactyly - intellectual deficit)
	Kocher - Deber - Semilange syndrome - (muscular pseudohypertrophy- hypothyroidism)
	Benign chorea - hypothyroidism
	Choreoathetosis - (hypothyroidism - neonatal respiratory distress) **NKX2.1 /TTF-1 mutation**
	Obesity - colitis - (hypothyroidism – cardiac hypertrophy - developmental delay)

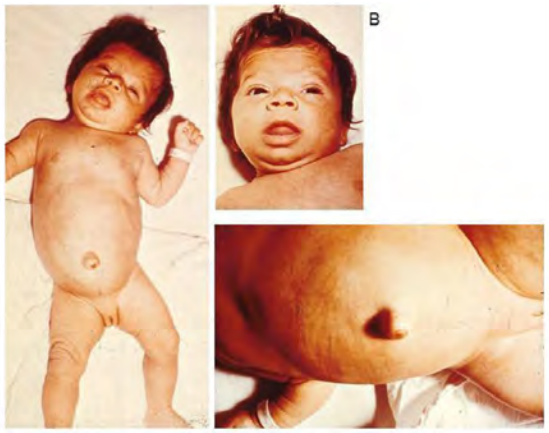
Rastogi &LaFranchi. Orphanet J Rare Diseas 2010

DEBUT IN PRIMA LUNA DE VIATA

- Cianoza periferica
- Detresa respiratorie
- Tulburari de supt
- Absenta cresterii in greutate
- Incetinirea tranzitului intestinal
- Activitate diminuata
- Letargie

DEBUT IN PRIMELE 3 LUNI

- Hernie ombilicala
- Constipatie
- Piele uscata si rece
- Macroglossie
- Edeme generalizate
- Strigat scurt si ragusit



- Nu tine capul la 2 luni
- Nu sta in sezut la 6 luni
- Nu merge la 10-12 luni
- Probleme de comunicare
- Retard mental ireversibil

ALTE SEMNE SI SIMPTOME

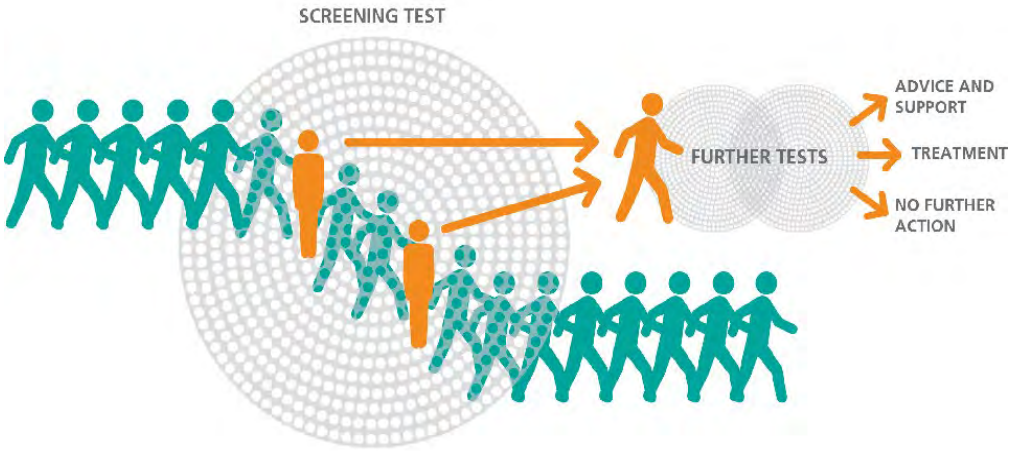
- Malformatii cardiace (defect septal atrial)
- 14% din copiii cu mixedem congenital prezinta malformatii cardiace si alte boli care se insotesc de intarziiere psiho-motorie
- Fetele cu mixedem congenital prezinta mai frecvent malformatii cardiace, anomalii congenitale ale SNC, muscular, gastrointestinal si urinar.

HIPOTIROIDIA CONGENITALA
doua scenarii

NORMOTHYROID MOTHER & HYPOTHYROID FETUS	HYPOTHYROID MOTHER & HYPOTHYROID FETUS
Ex: Thyroid dysgenesis	Ex: Iodine deficiency
1. Transplacental passage of hormones and 2. Increased Type-2 Deiodinase activity in fetal brain confer neuro protection.	These mechanisms are impaired.
Near normal cognitive outcome is possible if post natal therapy is initiated early.	Significant neuro-intellectual impairment occurs.

SCREENING

- Implementarea screening-ului universal al nou-nascutilor a inceput in anii ‘70.
- Detectarea cazurilor cu mixedem moderat a determinat o crestere dramatica a incidentei de la 1:4000 la 1:2000 de nou-nascuti in ultimii 20–30 de ani.



Cherella&Wassner, Int J Pediatr Endocrinol. 2017

Organization of the neonatal screening program for congenital hypothyroidism in Romania (Infant neonatal screening test for hypothyroidism, are included in the national register MEDILOG).

The information system MEDILOG was created by a team from "Alessandrescu-Rusescu" National Institute of Mother and Child Health in 2010

Regional Center Bucharest – INSMC „Alessandrescu-Rusescu"; Regional Center Iasi; Regional Center Timisoara; Regional Center Cluj; Regional Center Mures;

Nanu et al. Acta Endocrinologica, 2019

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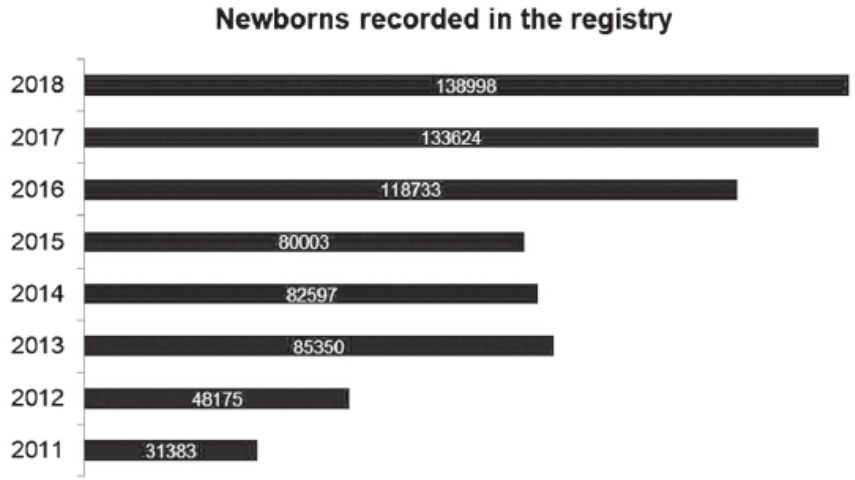
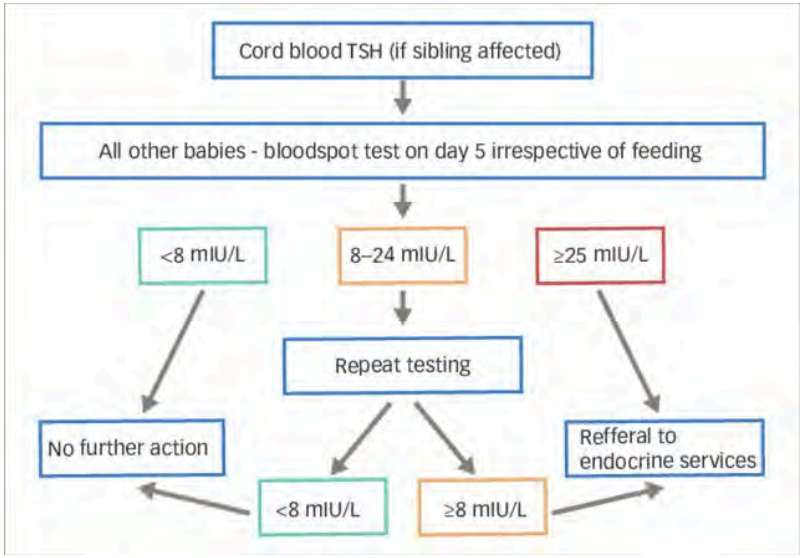


Year 2018	CH Confirmed	Total number of tested kids	Incidence
Cluj Regional Center	Data not available	27011	-
Iași Regional Center *	6	28474	1/4746
Mureș Regional Center **	2	8167	1/4083
Timiș Regional Center **	2	8679	1/4339
INSMC Bucharest Regional Center *	24	85841	1/3576

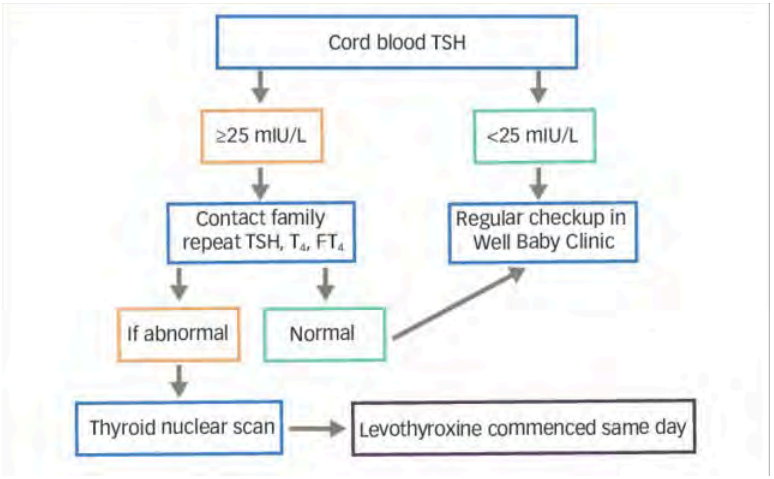
* MEDILOG data.

** Data reported at the Management Technical Assistance Unit Programme (UATMP) from INSMC.

Nanu et al. Acta Endocrinologica, 2019



Screening protocol (primary blood spot TSH)- National Health Service, Scotland



Screening protocol (cord blood TSH)- Christian Medical College and Hospital, Vellore

TSH CRESCUT. CAUZE

1. Permanent hypothyroidism

   Primary hypothyroidism (thyroid origin)
   Dysgenesis (agenesis, hypogenesis, ectopic thyroid gland, etc.)
   Dyshormonogenesis
   Peripheral thyroid hormone insufficiency
   Thyroid hormone resistance, thyroid hormone transporter abnormality (MCT8 defects), etc.
   Subclinical congenital hypothyroidism

   Others
   Loss of function mutations of TSH receptor gene
   Pseudohypoparathyroidism

2. Transient hypothyroidism (primary)
   Severe iodine deficiency
   Iodine excess
   Administration of anti-thyroid drugs to mother
   Loss of function mutations of DUOX2 gene, loss of function mutations of DUOXA2 gene

3. TSH-producing pituitary adenoma

4. Transient infantile hyperthyrotropinemia

5. Interference for TSH measurements
   Anti-TSH antibody, anti-mouse IgG antibody (HAMA), etc.

Nagasaki et al. Clin Pediatr Endocrinol. 2015

Table 3.1 Thyroid Hormone Reference Ranges (Mean ±SD) for Full Term and Preterm Neonates

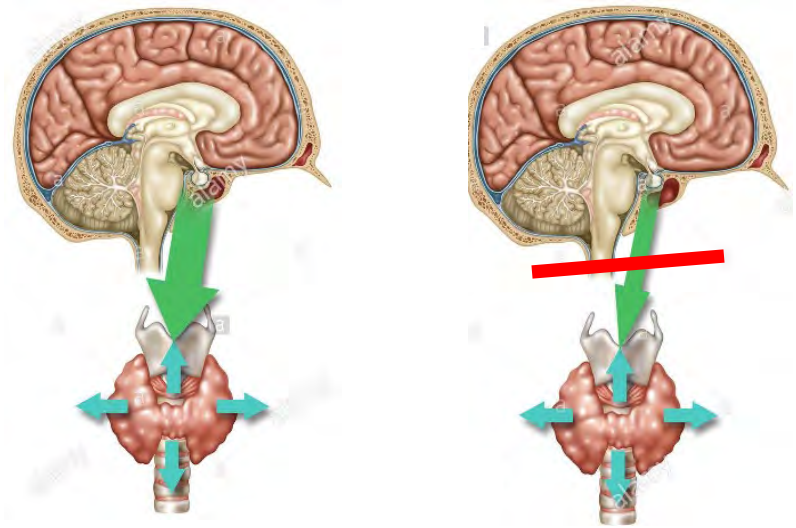
Gestational age (wks)	Age			
	Birth	7 days	14 days	28 days
Total T_4 (mcg/dL)				
23–27	5.4 ±2.0	4.0 ±1.8	4.7 ±2.6	6.1 ±2.3
28–30	6.3 ±2.0	6.3 ±2.1	6.6 ±2.3	7.5 ±2.3
31–34	7.6 ±2.3	9.4 ±3.4	9.1 ±3.6	8.9 ±3.0
≥37	9.2 ±1.9	12.7 ±2.9	10.7 ±1.4	9.7 ±2.2
Free T_4 (ng/dL)				
23–27	1.3 ±0.4	1.5 ±0.6	1.4 ±0.5	1.8 ±0.5
28–30	1.4 ±0.4	1.8 ±0.7	1.6 ±0.4	1.7 ±0.5
31–34	1.5 ±0.3	2.1 ±0.6	2.0 ±0.4	1.8 ±0.6
≥37	1.4 ±0.4	2.7 ±0.6	2.0 ±0.3	2.1 ±2.5
Total T_3 (ng/dL)				
23–27	19.5 ±14.9	32.6 ±20.2	41.0 ±24.7	63.1 ±27.3
28–30	28.6 ±20.8	56.0 ±24.1	72.3 ±28.0	87.2 ±31.2
31–34	35.2 ±23.4	91.8 ±35.8	109.4 ±41.0	119.8 ±40.1
≥37	59.9 ±34.5	147.8 ±50.1	167.3 ±31.2	175.8 ±31.9
TSH (mU/L)				
23–27	6.8 ±2.9	3.5 ±2.6	3.9 ±2.7	3.8 ±4.7
28–30	7.0 ±3.7	3.6 ±2.5	4.9 ±11.2	3.6 ±2.5
31–34	7.9 ±5.2	3.6 ±4.8	3.8 ±9.3	3.5 ±3.4
≥37	6.7 ±4.8	2.6 ±1.8	2.5 ±2.0	1.8 ±0.9

(continued)

Williams et al. J Clin Endocrinol Metab. 2004

ALTE TIPURI DE SCREENING

- **In Olanda TSH, T4 si TBG a dus la diagnosticarea hipotiroidiei congenitale centrale→ 1:16000 nn**
- **Avantaje: prevenirea hipoglicemiei severe (co-existenta deficit GH si/sau ACTH) si permite initierea precoce a tratamentului cu levotiroxina.**



Schoenmakers et al. J Endocrinol. 2015

HIPOTIROIDISMUL CONGENITAL TRANZITORIU

- **TSH ↑, fT4 si fT3↓**
- **Incidenta SUA intre 5% si 10% din copiii decelati prin screening (1:50000).**
- **Incidenta Franta 40% din copiii decelati prin screening**
- **Cauze: deficit de iod, ATS la mama, greutatea mica la nastere, exces de iod, transfer de la mama de TRAb.**

Nagasaki et al. Clin Pediatr Endocrinol. 2015

TSH ↑ TRANZITOR

- **TSH ↑, fT4 si fT3 normale**
- **Crestere indusa de frig (in ziua 1 si 2 de viata)**
- **TSH se normalizeaza in perioada de sugar**
- **Nu se deceleaza nici o cauza de hipotiroidism**
- **Tiroida normala ecografic si scintigrafic**

Nagasaki et al. Clin Pediatr Endocrinol. 2015

HIPERTIROTROPINEMIA IZOLATA

- TSH↑ si T4 normal
- Indica o productie inadecvata de hormoni tiroidieni.
- Este mai frecventa la prematuri.
- Cauze: deficit iodat, medicatie la mama, disgenezii tiroidiene.
- Valorile crescute ale TSH (cu fT4 normal) pot persista ani de zile.

Buyukgebiz, J Clin Res Pediatr En docrinol. 2013

HIPOTIROXINEMIA

- T4↓ si TSH normal
- Mai frecvent la copii prematuri (la 50% din cei nascuti sub 30 saptamani).
- Fractia libera este mai putin afectata decat T4
- Cauze: imaturitate ax hipotalamo-hipofizar, TBG↓ (maladie genetica X-linkata), conversie ↓ T4-T3
- Alte cauze: euthyroid sick syndrome (denutritie, imaturitate hepatica), eroare de laborator, hipotiroidie centrala.

Buyukgebiz, J Clin Res Pediatr En docrinol. 2013

European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism

Juliane Léger, Antonella Olivieri, Malcolm Donaldson, Toni Torresani, Heiko Krude, Guy van Vliet, Michel Polak, and Gary Butler, on behalf of ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE, and the Congenital Hypothyroidism Consensus Conference Group

1.3 Screening in special categories of neonates at risk of CH

- A strategy of second screening should be considered for the following conditions: preterm neonates; low-birth weight (LBW) and very low-birth weight (VLBW) neonates; ill and preterm newborns admitted to neonatal intensive care units (NICU); specimen collection within the first 24 hours of life; and multiple births (particularly same-sex twins); (2|⊕⊕○).

Repetarea testului la varsta de 14 zile sau la 14 zile dupa primul test (toate valorile trebuie analizate in functie de metoda folosita, valorile normale pentru fiecare parametru-TSH, fT4, varsta copilului si varsta gestationala).

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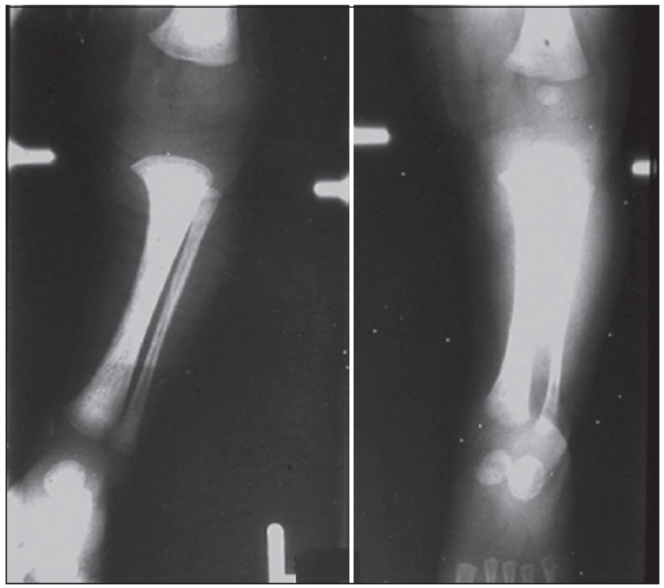
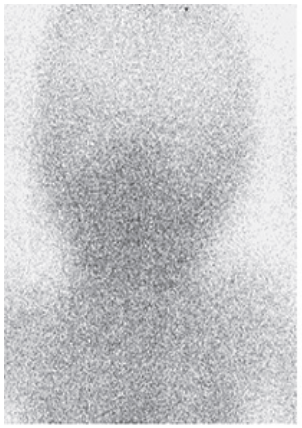
2.4 Use of imaging in assessing the severity and cause of CH

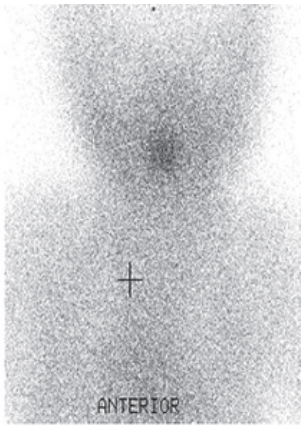
- X-ray of the knee may be carried out to assess the severity of intrauterine hypothyroidism by the presence or absence of femoral and tibial epiphyses (2|⊕⊕⊕).
- The thyroid gland should be imaged using either radioisotope scanning (scintigraphy) with or without the perchlorate discharge test; or ultrasonography; or both (1|⊕⊕○).
- Imaging should never be allowed to delay the initiation of treatment (1|⊕⊕○).

2.5 Associated malformations and syndromes

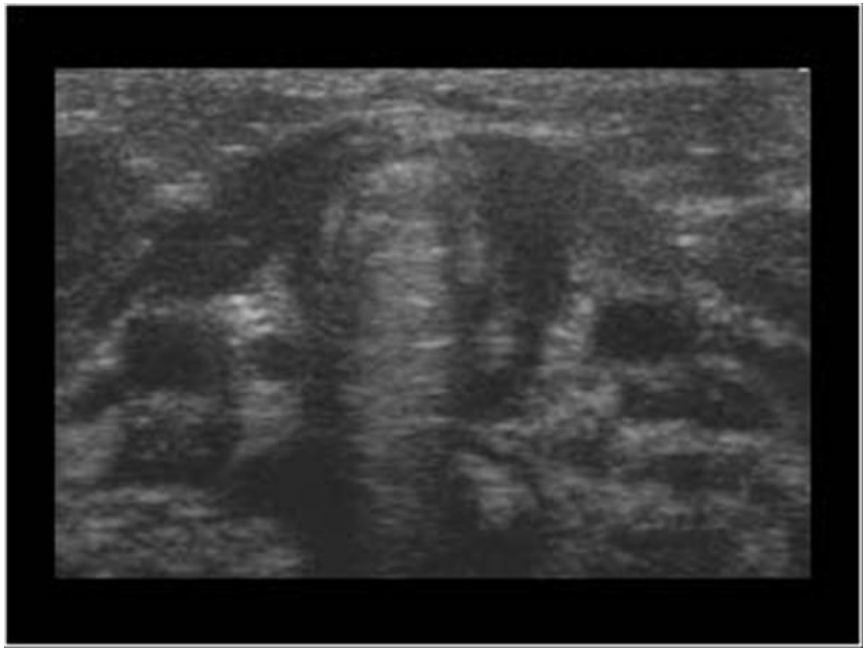
- All neonates with high TSH concentrations should be examined carefully for congenital malformations (particularly cardiac) and for dysmorphic features (1|⊕⊕⊕).







The left lower extremity of two infants; absent distal femoral epiphysis on left while in the normal infant on the right the distal femoral epiphysis is present



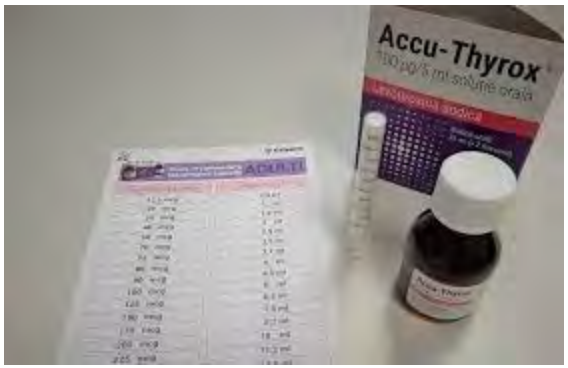
Age of the children	Thyroxine dose, μg/kg/day (μg/day)
CH	10-15 (~37.5-50)
Before 6 months	8-10 (~25-37.5)
After 6 months	
6-12 months	6-8 (~50-75)
1-5 years	5-6 (~75-100)
6-12 years	4-5 (~75-125)
12 years to adult	1-3 (~100-200)
Infantile CH	8-10 (~25-37.5)
Juvenile and adult CH	1.3

Unnikrishnan &Vyas. Thyroid Res Pract 2017

➢Atat levotiroxina sub forma de tableta sau lichida normalizeaza fT4 in 7-10 zile de la administrare.

➢La noi-nascutii cu forme severe si moderate forma lichida este absorbita mai bine comparativ cu tb (Yue et al. concentratie maxima la 30 min dupa administrare).

➢Formula lichida este mai usor de administrat si doza poate fi individualizata cu mai mare usurinta.



Unnikrishnan &Vyas. Thyroid Res Pract 2017

Follow-up treatment	AAP	ESPE	APEG	La Franchi, 2011[29]
Initiation of treatment	2-4 weeks	1-2 weeks	2-6 weeks	2-4 weeks
During 1st year	1-2 months	1-3 months	3 months interval	Every 1-2 months
During 2nd and 3rd year	Every 2-3 months	Every 2-4 months	3 months interval	Every 2-3 months
Thereafter or until growth complete	3-12 months until growth and puberty complete	Every 3-12 months	4 months	6-12 months

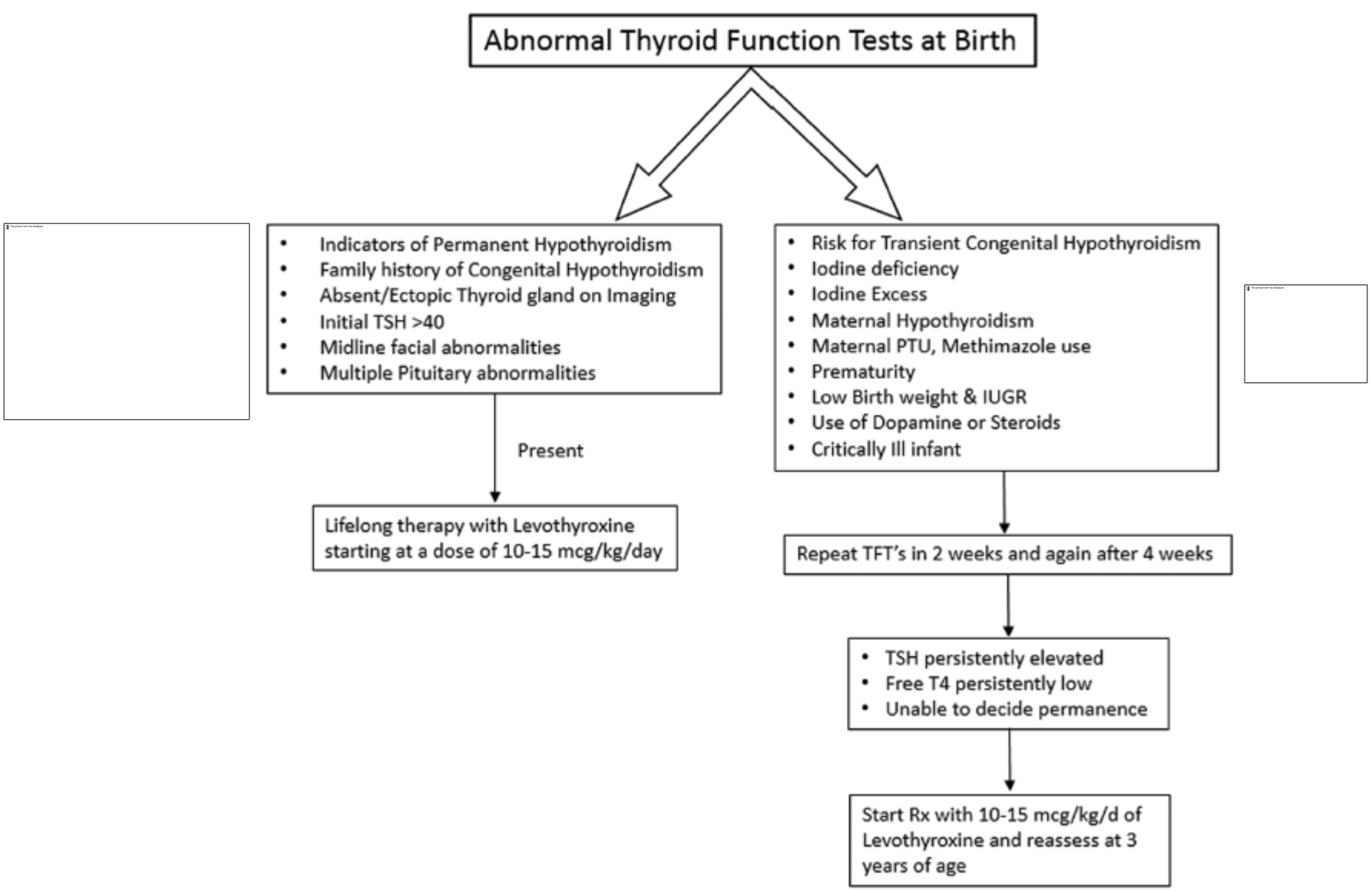
AAP: American Academy of Pediatrics, ESPE: European Society for Pediatric Endocrinology, APEG: Australian Pediatric Endocrine Group

Unnikrishnan &Vyas. Thyroid Res Pract 2017

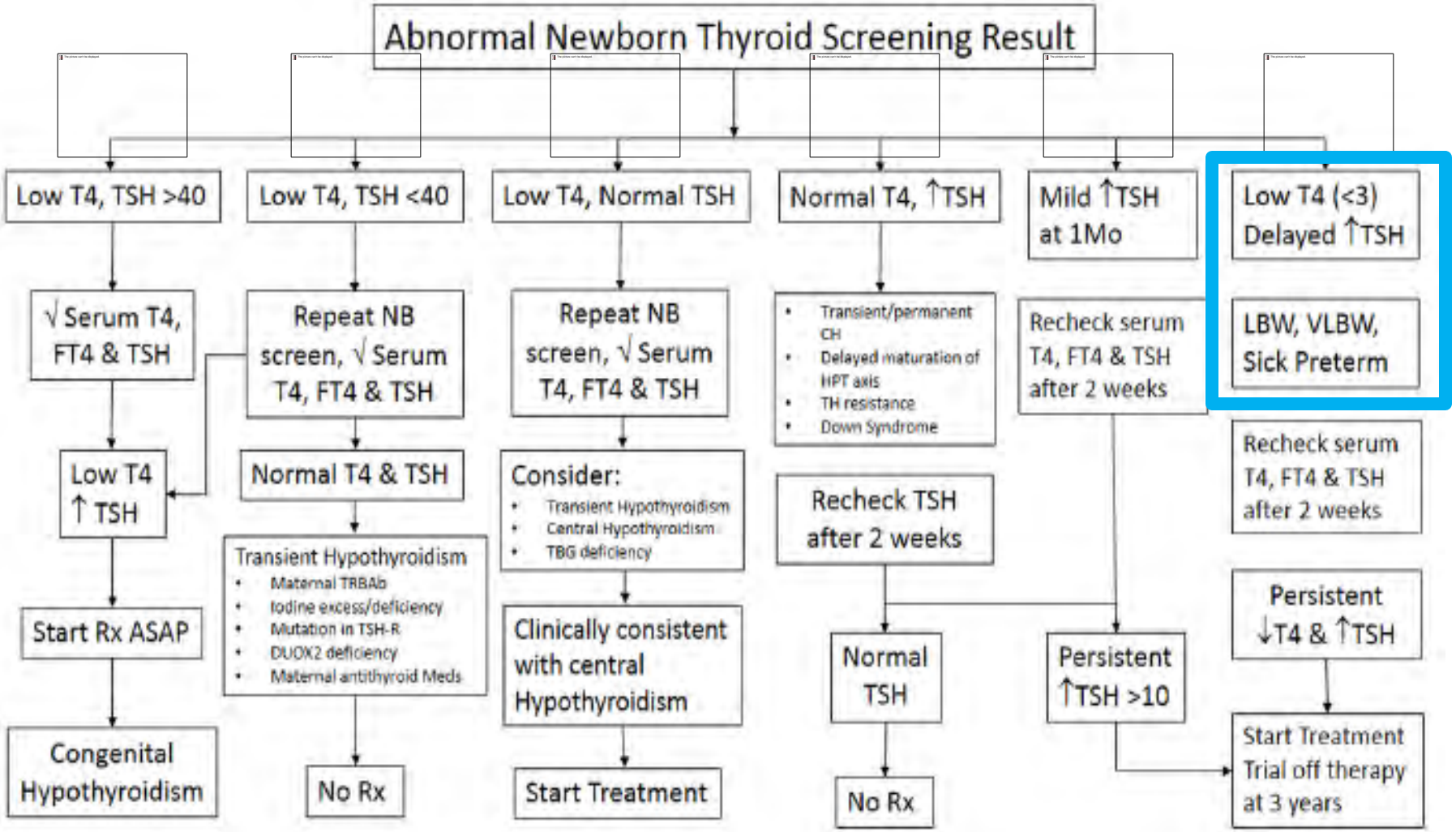
TRATAMENTUL IN HIPOTIROIDIA CONGENITALA CENTRALA

- **Doza substitutiva de tiroxina se va administra in functie de valoarea fT4.**
- **fT4 trebuie mentinut in intervalul de jumatate superioara a normalului**
- **Dozarea fT3 este mai sensibila in decelarea celor supradozati**

Schoenmakers et al. J Endocrinol. 2015



Kanike et al. Transl Pediatr. 2017



Kanike et al. Transl Pediatr. 2017

INTREBAREA 1

Fetele cu mixedem congenital prezinta mai frecvent:

a. malformatii cardiace?

sau

b. malformatii ale organelor genitale?

INTREBAREA 2

Care sunt categoriile speciale de nou-nascuti la care se recomanda al doilea screening pentru mixedemul congenital?

a. Prematuri
b. NN cu greutate mare la nastere
c. NN proveniti din sarcini supramaturate
d. NN cu greutate mica la nastere
e. Gemeni de acelasi sex

CONCLUZII

- In ultimii 50 de ani s-au obtinut rezultate extraordinare in ceea ce priveste: diagnosticul, tratamentul si evolutia pacientilor cu mixedem congenital.
- Patogenia ➡ ⬅ componenta genetica (multiple variante ale genelor implicate in fiziologia si morfologia tiroidiana).
- Ghidurile existente trebuie perfectionate in ceea ce priveste managementul hipotiroidiei congenitale moderate.