

Een afwijkende screening voor CH; en dan....?

Nitash Zwaveling-Soonawala

Kinderarts-endocrinoloog, Emma Kinderziekenhuis AMC



Indeling

- Waarom CH screening
- Ontwikkeling/werking vd schildklier
- Etiologie CH
- Work-up CH
- Casuïstiek CH
- Behandeling CH



Waarom screening op CH?

- Platter, 1602:

Zwitserse arts en psychiater, 1536-1614

1^e beschrijving "endemisch cretinisme"

"In Bremis, a village of the Valais, as I have seen myself, and in a valley in Carinthia called Bintzgerthal, it is usual that many infants suffer from innate folly"

"Besides, the head is sometimes misshapen; the tongue is huge and swollen; they are dumb; the throat is often goitrous..."

Cranefield BF. The discovery of cretinism.
Bull Hist Med 1962;36:489-511



Waarom screening op CH?

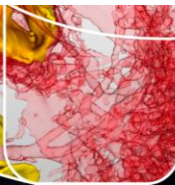
- Curlings, 1850:

1^e beschrijving sporadische congenitale hypothyreoïdie

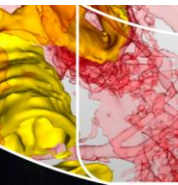
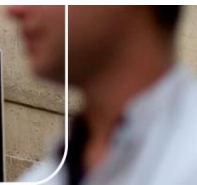
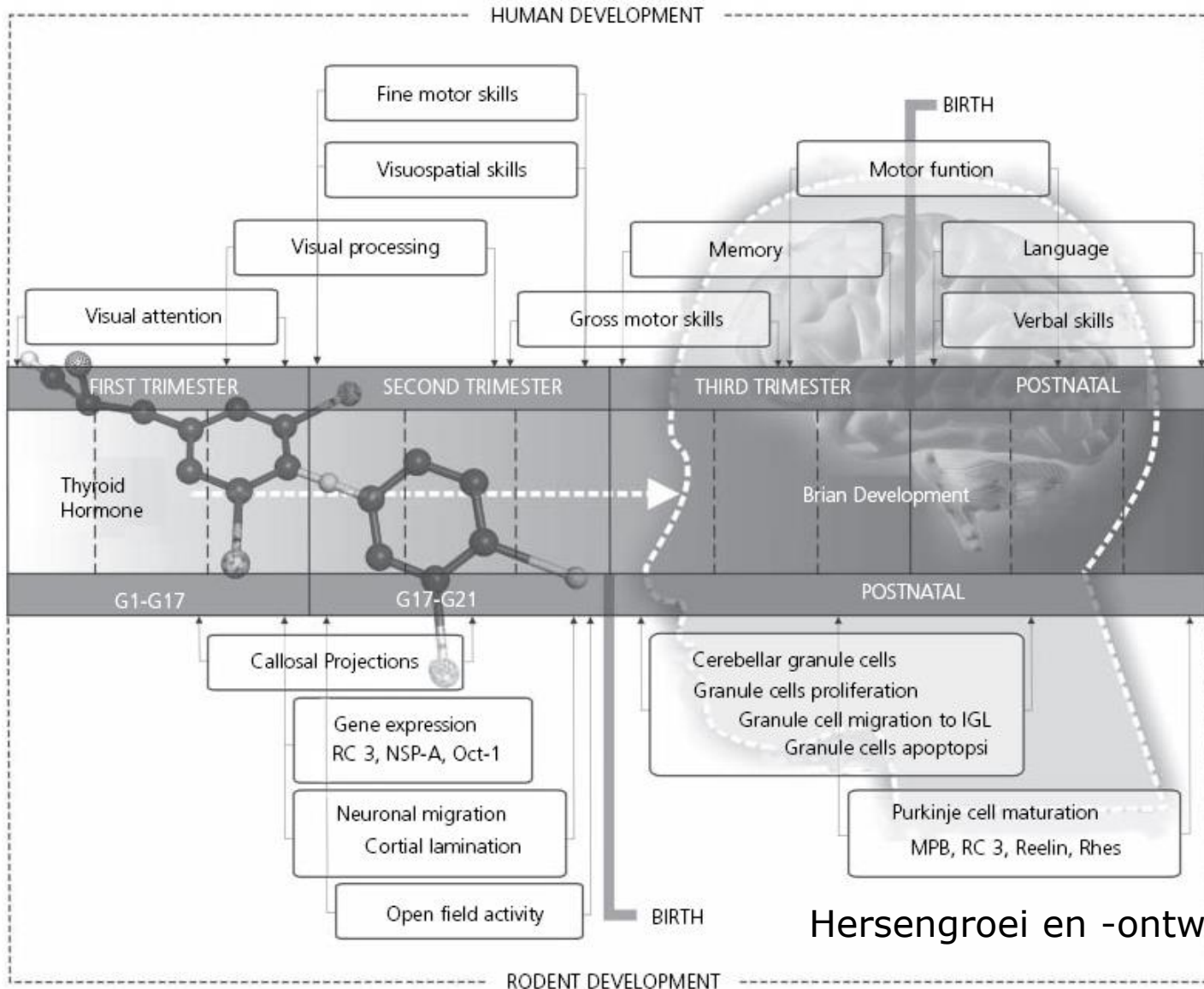
"2 mentally retarded children with large tongues and idiotic expressions"

"at autopsy no thyroid tissue could be found"

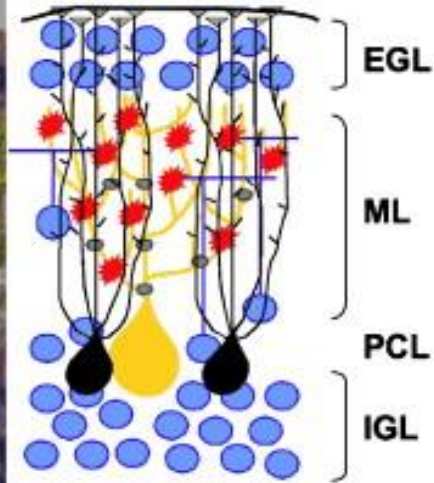
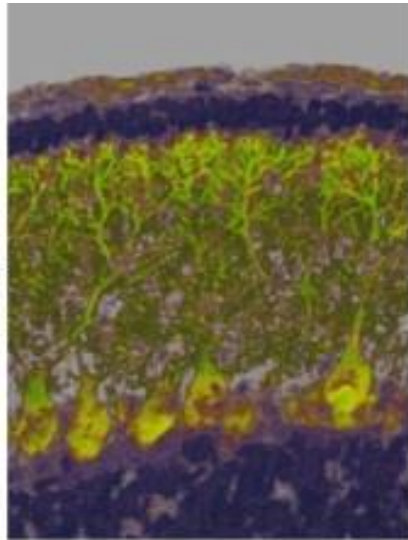
Curling TB. Two cases of absence of the thyroid body and symmetrical swelling of fat tissue at sides of neck with defective cerebral development. Med Chirurg Tr 1850, 33:303-306.



Timing of thyroid hormone action in the developing brain

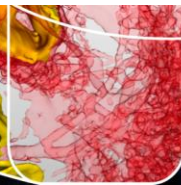
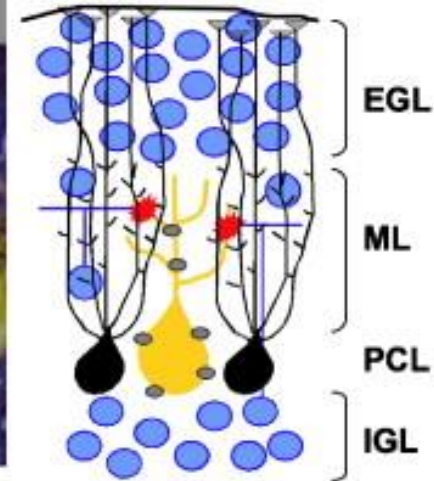
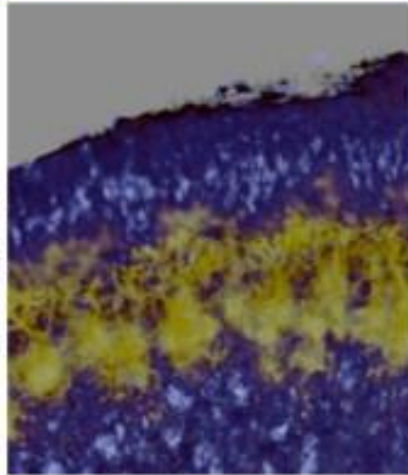


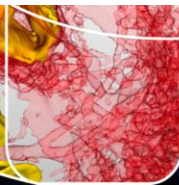
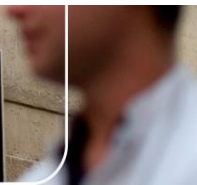
euthyroid



mouse cerebellar cortex P12

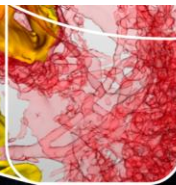
hypothyroid



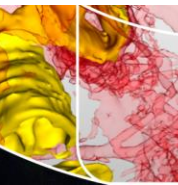
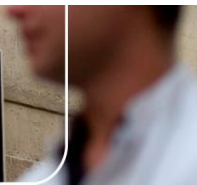
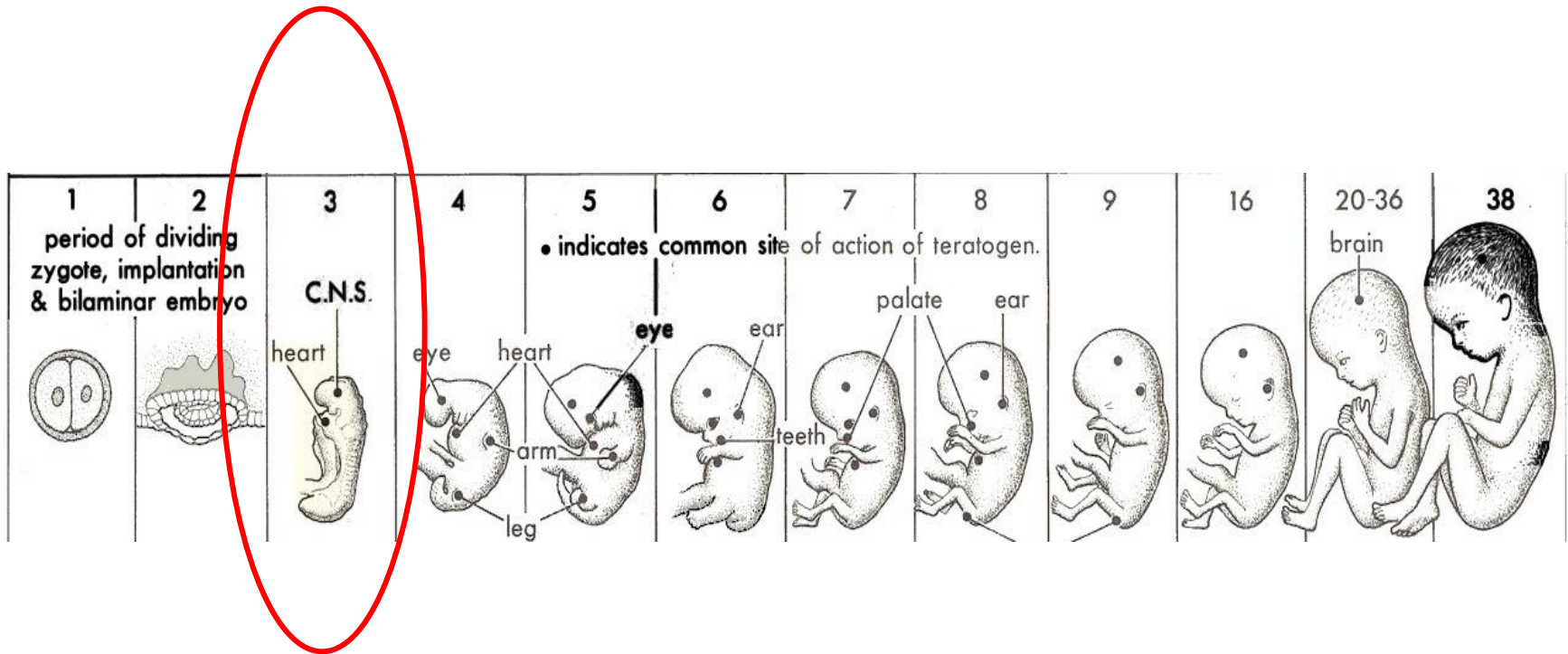


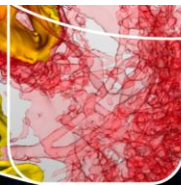
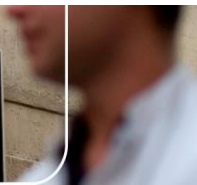
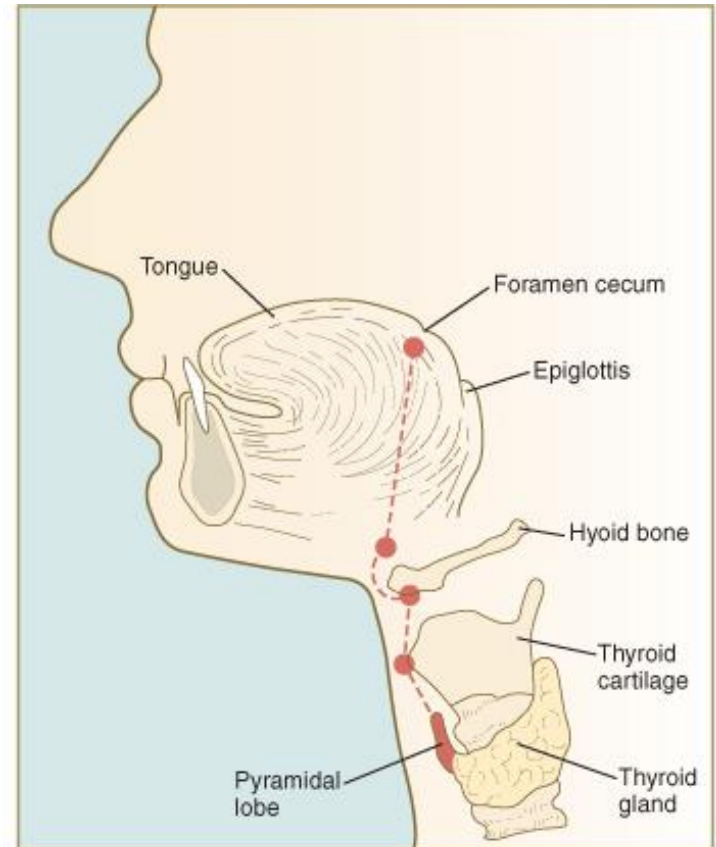
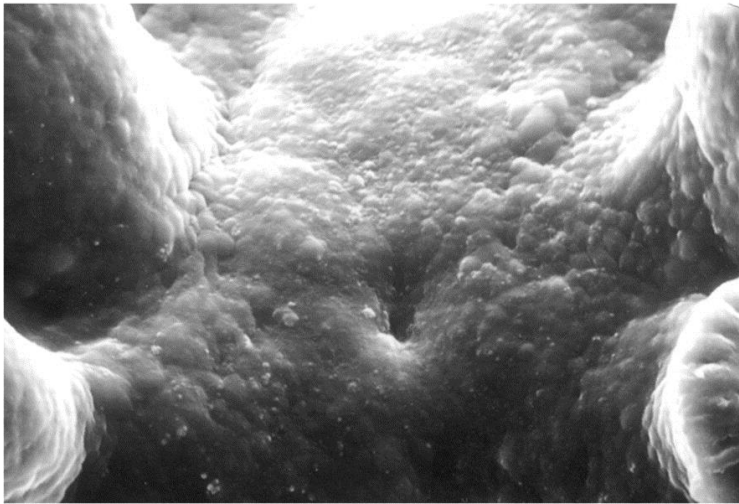


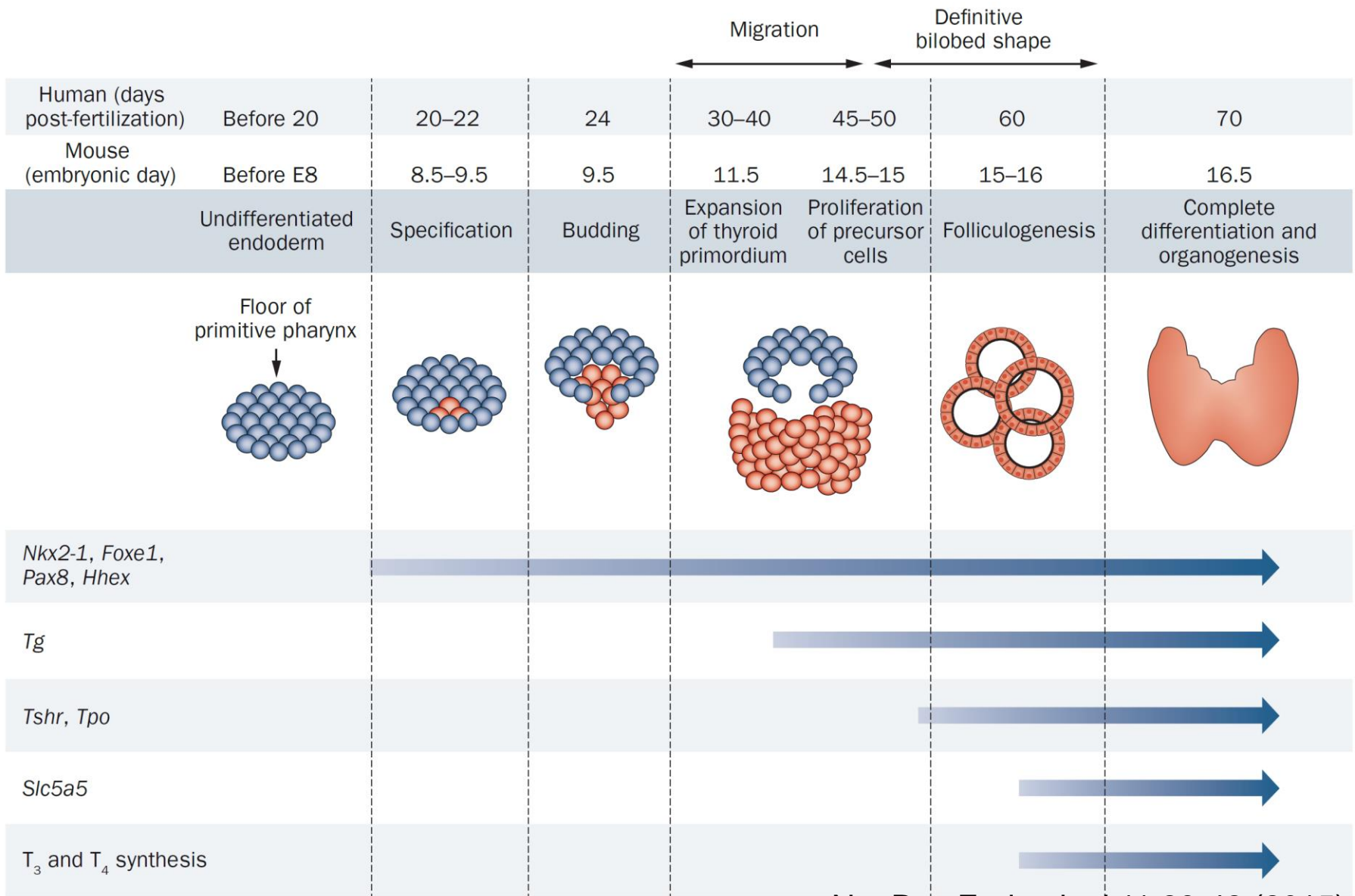
- Verlengde icterus
- Open achterste fontanel
- Macroglossie
- Opgezette buik
- Hernia umbilicalis
- Slecht drinken
- Oedeem (periorbitaal, pretibiaal)
- Hypotonie
- "Schorre" huid



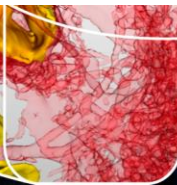
Ontwikkeling van de schildklier

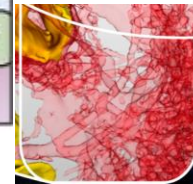
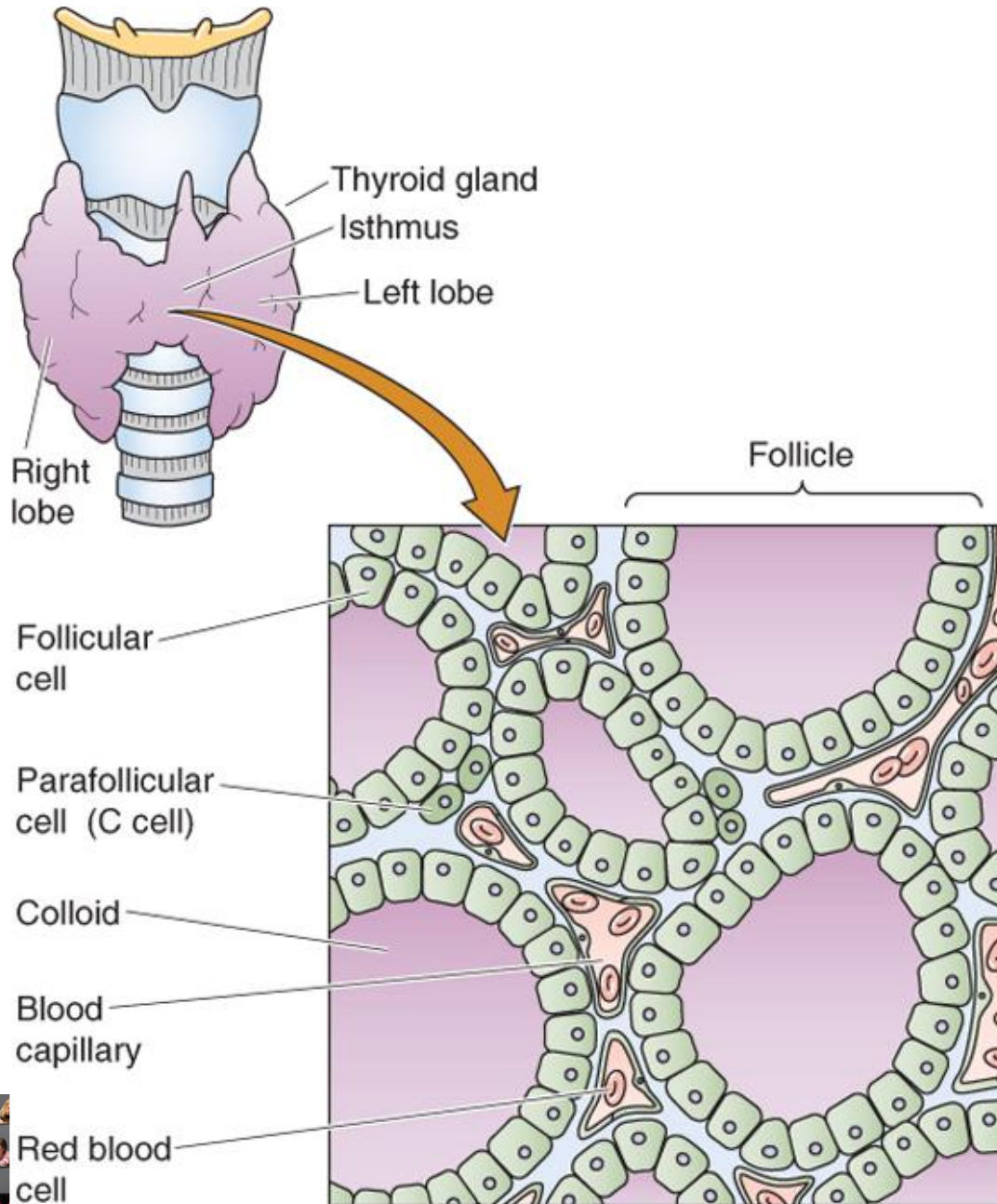




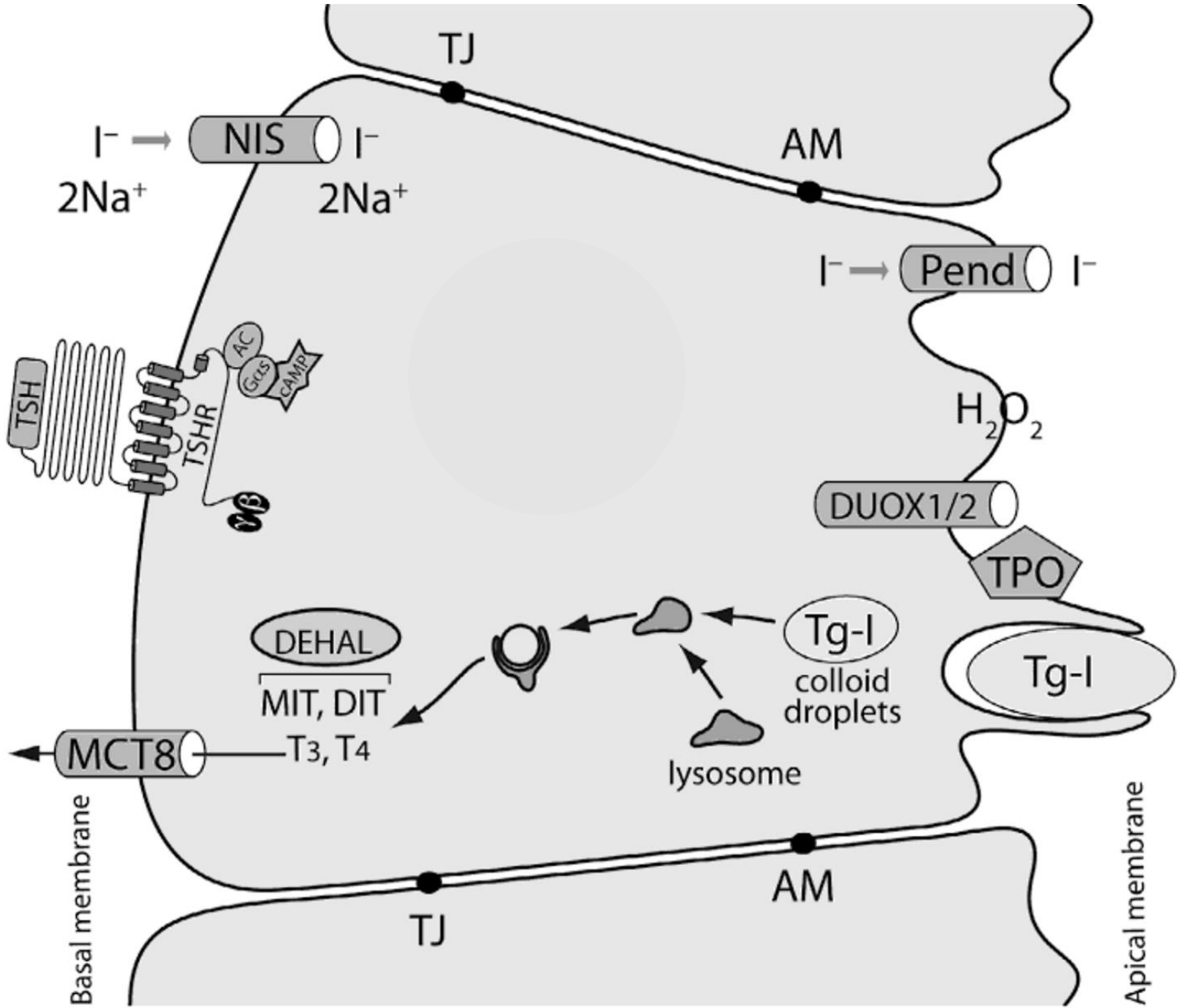


Nat Rev Endocrinol 11;29-42 (2015)



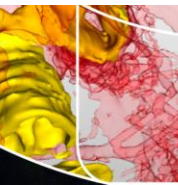
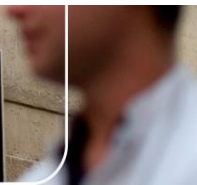
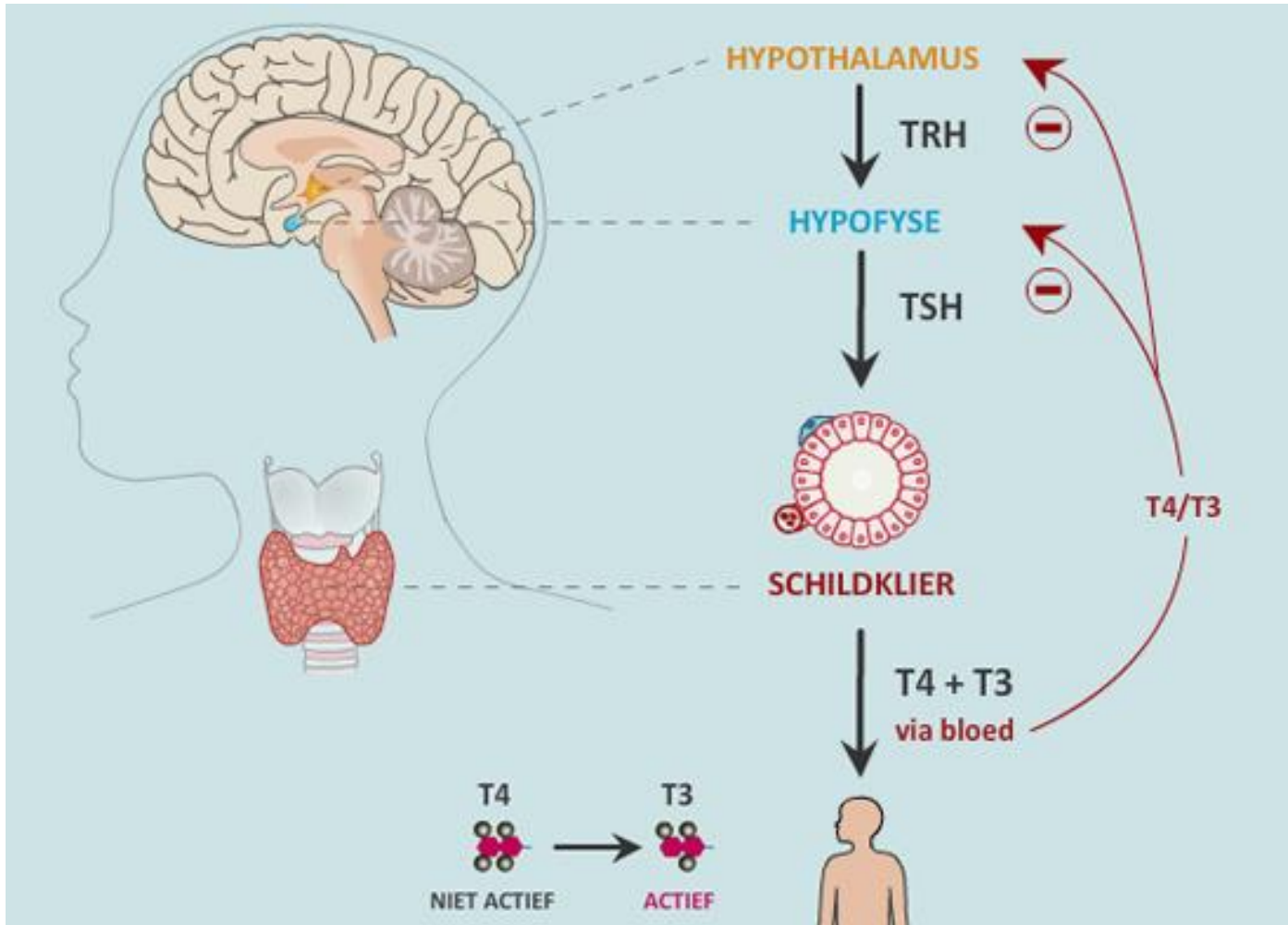


B L O O D
S T R E A M



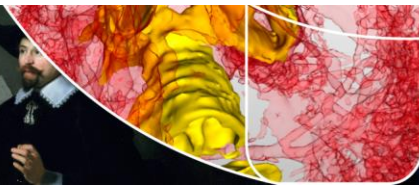
C O L L O I D





Oorzaken van CH

- Stoornis in de aanleg van de schildklier
“dysgenesie/agenesie”
 - Stoornis in de aanmaak v. schildklierhormoon
“dyshormogenese”
 - Stoornis in de aansturing van de schildklier door de hypofyse
“hypofyse insufficiëntie”
- = Primaire CH
90%
CH-T**
- = Centrale CH
10%
CH-C**



Aanlegstoornissen

- Agenesie
- Dystopie:
bv. sublinguaal rudiment
- Hypoplasie
 - TSH-R mutaties

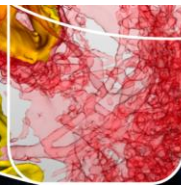
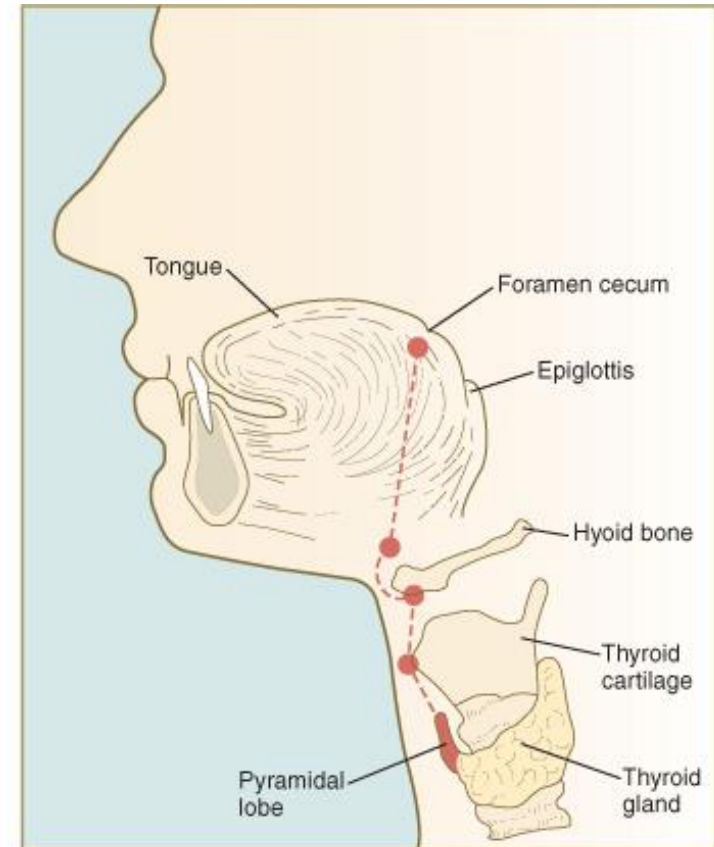


Table 3 | Human phenotypes and syndromes associated with mutations in TTF-encoding genes

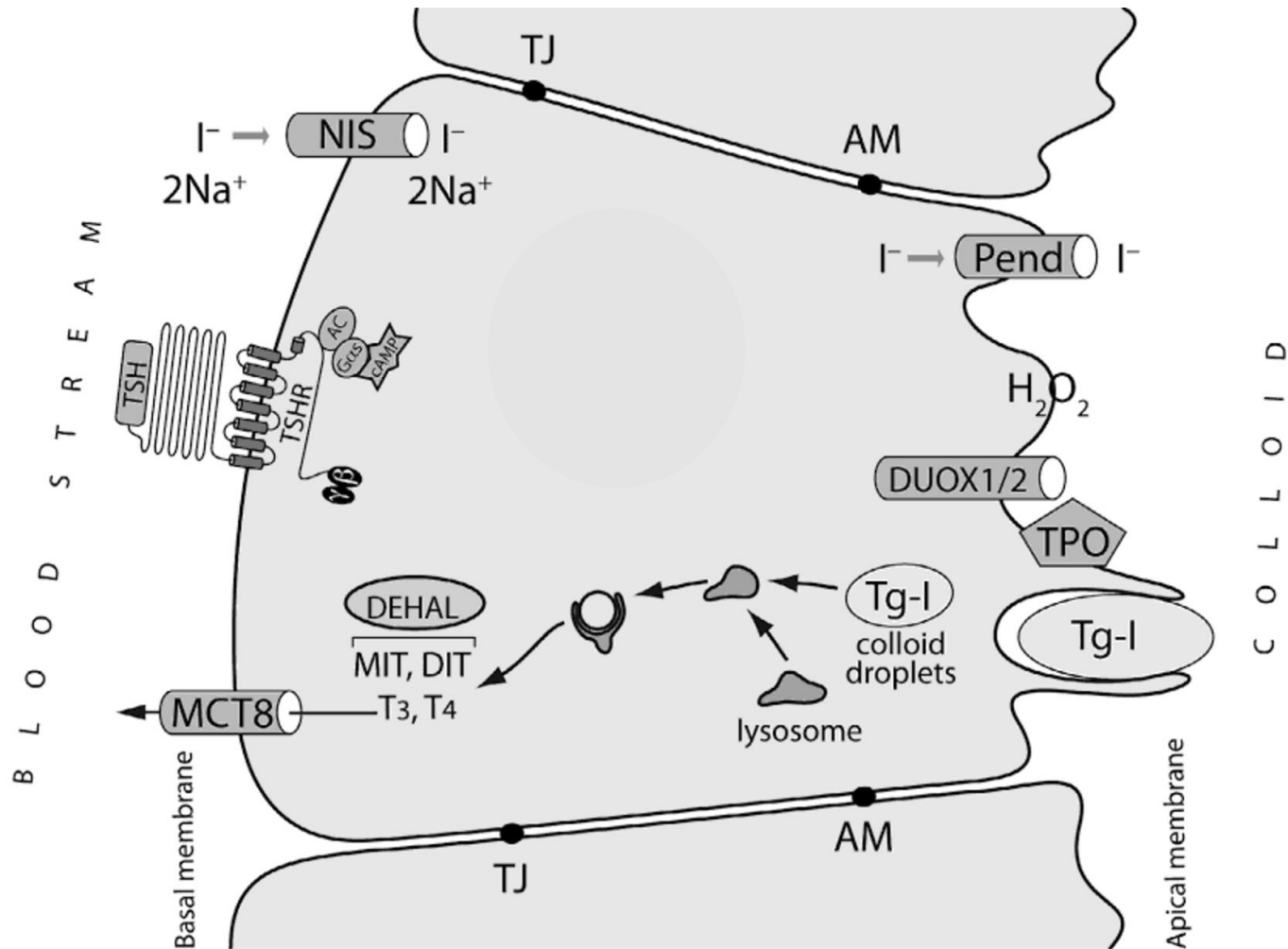
TTF gene	Mutation location	Phenotype	Disease
<i>NKX2-1</i>	Homeobox or region encoding the transactivation domain	Normal thyroid, thyroid agenesis, athyreosis, hypoplasia, hemiagenesis and/or benign hereditary chorea and respiratory distress ^{126–129}	Brain–lung–thyroid syndrome ¹³⁰
<i>FOXE1</i>	Forkhead box	Thyroid hypoplasia, athyreosis and/or cleft palate, choanal atresia, bifid epiglottis, spiky hair and tongue-tie ¹³⁴	Bamforth–Lazarus syndrome ²¹
	Polymorphisms determining the length of the polyalanine tract	Thyroid ectopia ^{136,137} and hemiagenesis ¹³⁸	Thyroid dysgenesis
<i>PAX8</i>	Paired box, region encoding the transactivation domain, or promoter region	Thyroid hypoplasia, athyreosis, thyroid ectopia ¹⁴⁵ and, rarely, unilateral kidney ¹⁴⁷ and problems in urogenital tract ¹⁴⁶	Congenital hypothyroidism due to thyroid dysgenesis ¹²⁶
<i>HHEX</i>	No mutations identified in humans	None	None

Abbreviation: TTF, thyroid transcription factor.

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Dyshormogenese



Werner Ingbar; Thyroid 2013

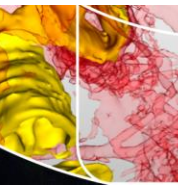
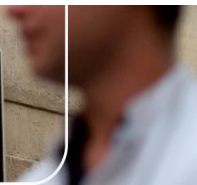
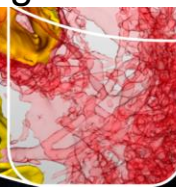


Table 1. Thyroid Ultrasound, Scintigraphy, and Serum Thyroglobulin Findings in Thyroid Dysgenesis, Dyshormonogenesis, and Some Forms of Transient CH

Defect	Thyroid Ultrasound	Thyroid Scintigraphy	Serum Thyroglobulin Concentration
Thyroid dysgenesis			
Apparent athyreosis	No thyroid tissue seen	No uptake	Detectable ($\geq 2 \mu\text{g/L}$)
True athyreosis	No thyroid tissue seen	No uptake	Undetectable
Ectopy	Either no thyroid tissue seen or ectopic tissue seen (especially if in a sublingual or perihyoid location)	Uptake into ectopic gland	Usually \uparrow but may be N or \downarrow
Hypoplasia in situ	Small eutopic gland	Low level of uptake in a normally sited gland	N or \downarrow
Hemiagenesis	Hemithyroid	Hemithyroid	N
Dyshormonogenesis			
NIS/SCL5A5	Enlarged gland	Uptake absent or $\downarrow\downarrow$	\uparrow
Thyroid peroxidase, TPO	Enlarged gland	High level of uptake; positive perchlorate discharge test	$\uparrow\uparrow$
Dual oxidase 2, DUOX2/dual oxidase 2 maturation factor, DUOXA2	Enlarged gland	High level of uptake; positive perchlorate discharge test	\uparrow
Thyroglobulin, TG	Enlarged gland	Avid uptake; normal perchlorate discharge test	$\downarrow\downarrow$ or undetectable
Pendred syndrome, pendrin PDS/ SCL26A4	Normal/enlarged gland	High level of uptake; positive perchlorate discharge test	\uparrow
Dehalogenase, IYD/ DEHAL1	Enlarged gland	Avid uptake; normal perchlorate discharge test	\uparrow

ESPE guidelines JCEM 2015



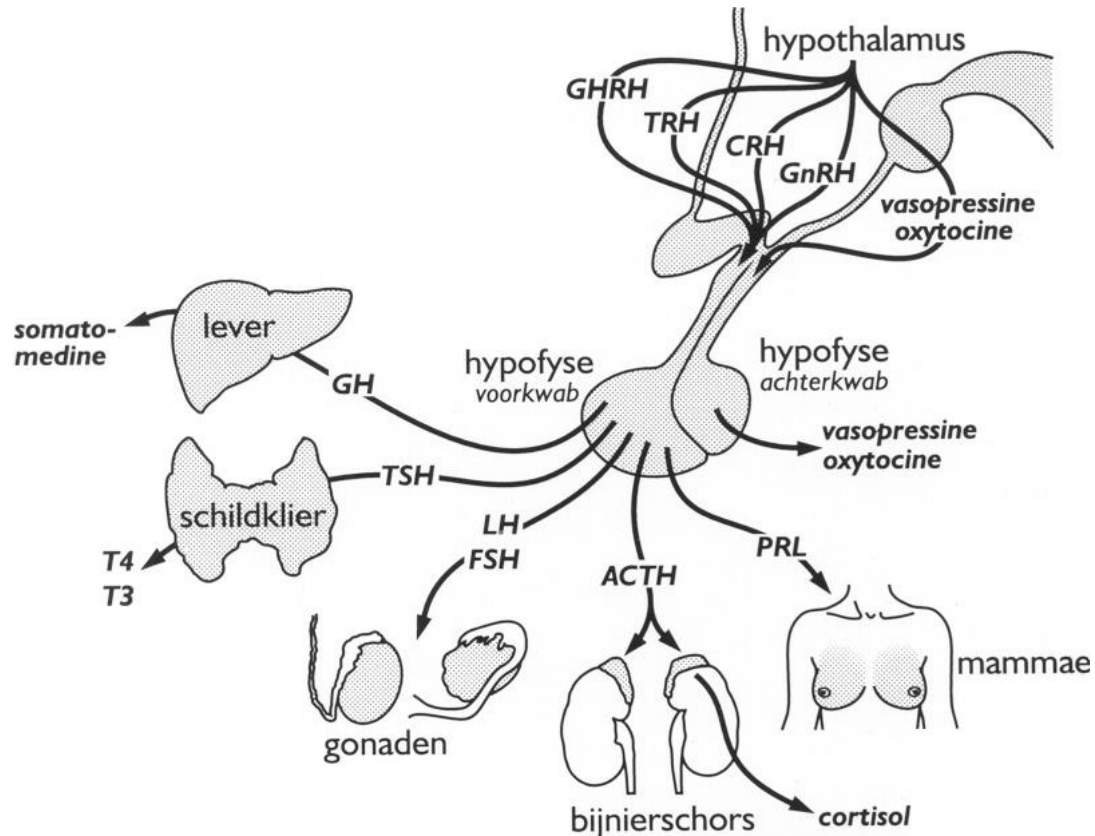
Dyshormogenese

- Kans op struma
- Meestal autosomaal recessief
 - 25% herhalingskans



Centrale hypothyreoïdie (CH-C)

- Geïsoleerde centrale CH (20%)
- Multipele hypofyse uitval (80%)



CH-C

- Zeldzaam: 1/16.000 pasgeborenen (CH-T 1/2.500)
- Echter potentieel levensbedreigend
 - Bij MPHD 50% ook bijnierschorsinsufficiëntie
 - Risico op hypoglykemieën, irreversibele hersenschade



Neonatale CH screening

- In NL sinds 1981
- Wereldwijd TSH screening
- Unieke screening: primaire **T4** meting met follow-up TSH en TBG meting
- Zowel primaire hypothyreoïdie als centrale hypothyreoïdie opgespoord.



Work-up CHT

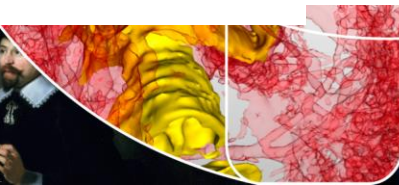
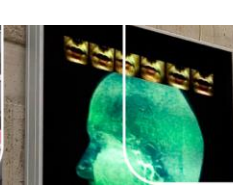
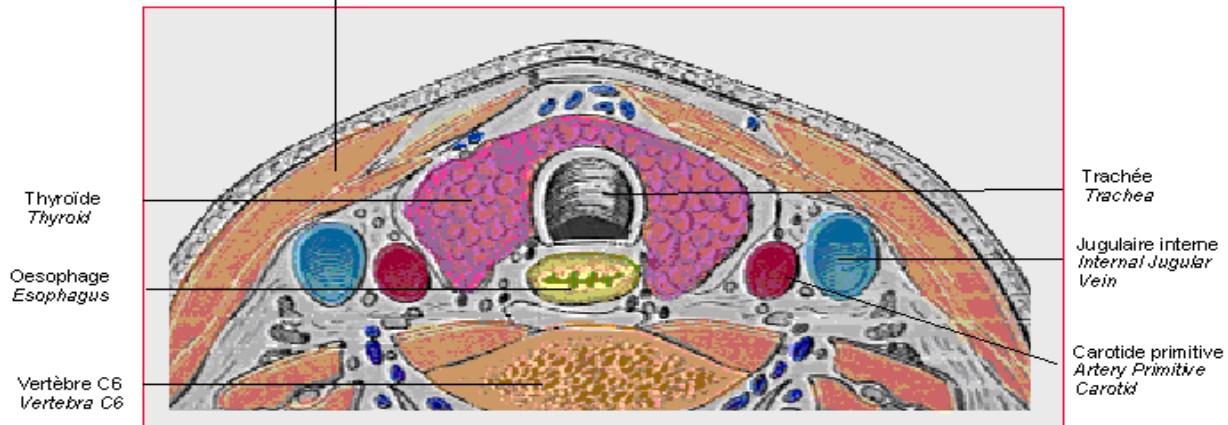
- Anamnese:
 - Zwangerschapsduur / geboorte gewicht
 - Maternale schildklierziekte (evt moeder prikken)
 - Ziekte kind, blootstelling jodium
- Lichamelijk onderzoek:
 - struma
- Venapunctie:
 - **TSH, vrijT4**
 - thyreoglobuline, TBG, TSH-receptor antistoffen



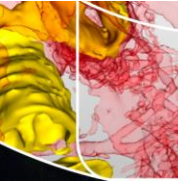
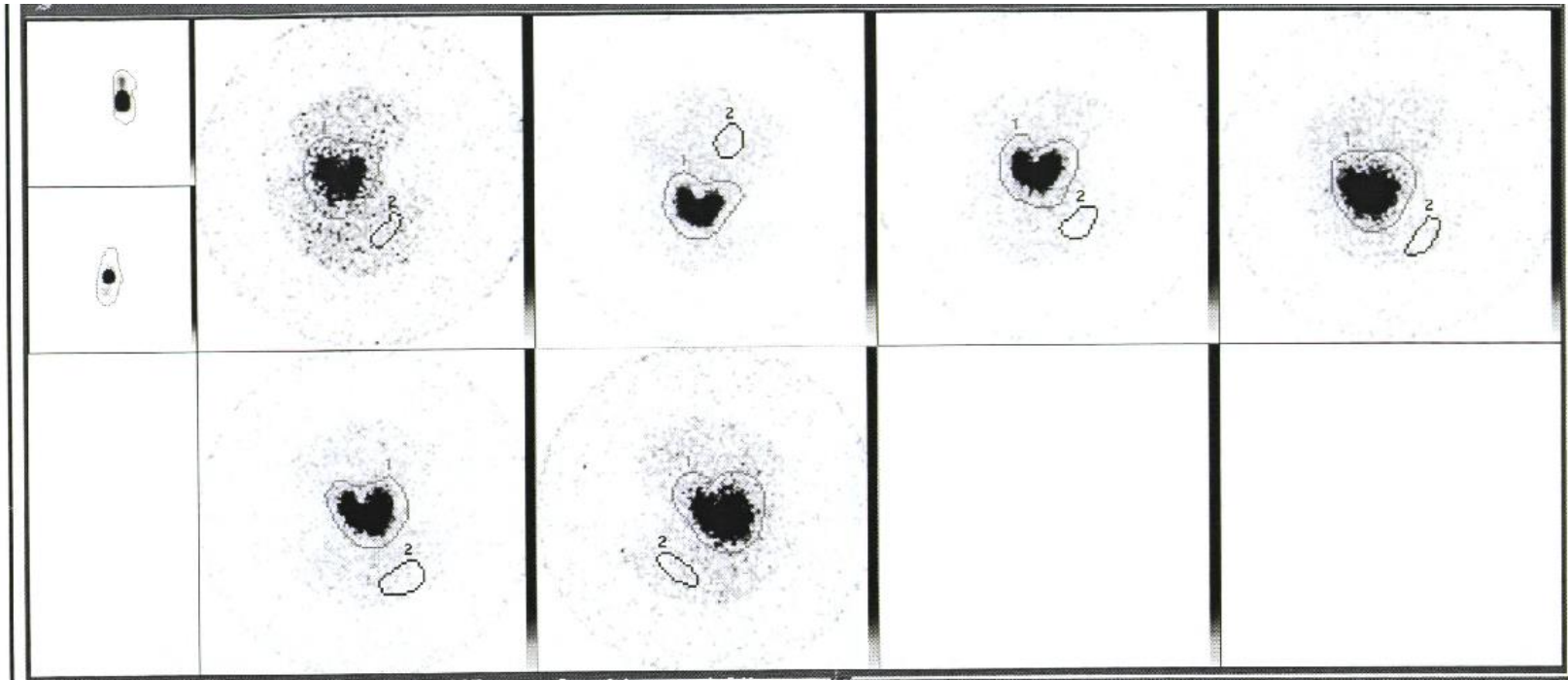
Beeldvormend onderzoek: Echo



Muscle sternocleidomastoidien
Sternocleidomastoid Muscle



123-jodide scan



Perchloraat wash-out test

- Meten van uitwas 123-jodide na toediening perchloraat
- Hoge uitwas wijst op organificatie stoornis



- TSH > 20
- Pitfalls scan:
 - TSH niet hoog genoeg
 - maternale TSH-R blokkerende antistoffen
 - NIS
 - TSH-R mutatie


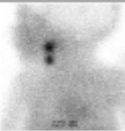




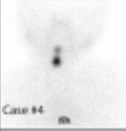
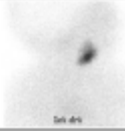

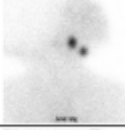
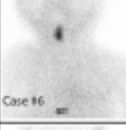
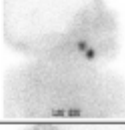

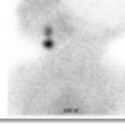


Combined ultrasound and isotope scanning is more informative in the diagnosis of congenital hypothyroidism than single scanning

R J Perry, S Maroo, A C Maclennan, J H Jones, M D C Donaldson

Arch Dis Child 2006



ANTERIOR VIEW	LATERAL VIEW	AT BIRTH		AT NEONATAL SCREENING		AT SCINTIGRAPHY				
		Sex	Weight (g)	TSH (mIU/L) < 15*	Total T4 (nmol/L) 120-350*	Age (days)	TSH (mIU/L) 0.4-11*	Free T4 (pmol/L) 11-23*	Tg (µg/L) < 20*	
		F	3000	53	149	11	118.0	9.6	61.7	
		F	3380	24	136	20	52.7	9.2	313.0	
		M	3780	23	158	42	15.4	9.7	418.8	
		M	3900	179	111	13	187.0	6.3	218.3	
		F	3870	138	142	13	112.2	8.0	143.9	
		F	4310	235	70	11	442.7	5.9	69.3	
		M	4340	35	110	19	28.7	10.7	NA	
		Medians		3870	53	136	13	112.2	9.2	181.1

* Normal values

FIG. 1. Evidence for dual thyroid ectopy by ^{99m}Tc sodium pertechnetate scintigraphy (cases 1-7) with relevant clinical and biological variables. Tg, Thyroglobulin.

J Clin Endocrinol Metab, June 2012, 97(6):E978-E981

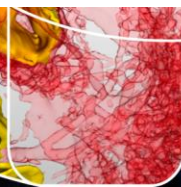
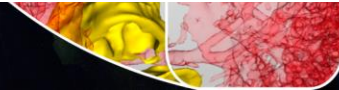
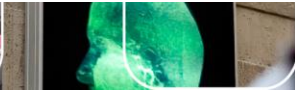


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Work-up CHC

- Diagnose obv te lage FT4 (wat is te laag?)
- ivm mogelijke bijnierschorsinsufficiëntie opname geïndiceerd (glucose controles)
- Altijd overleg met kinderendocrinoloog



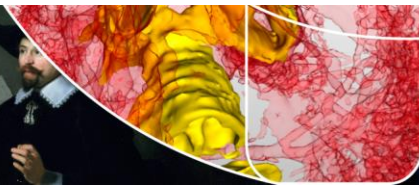
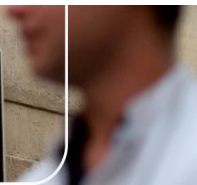
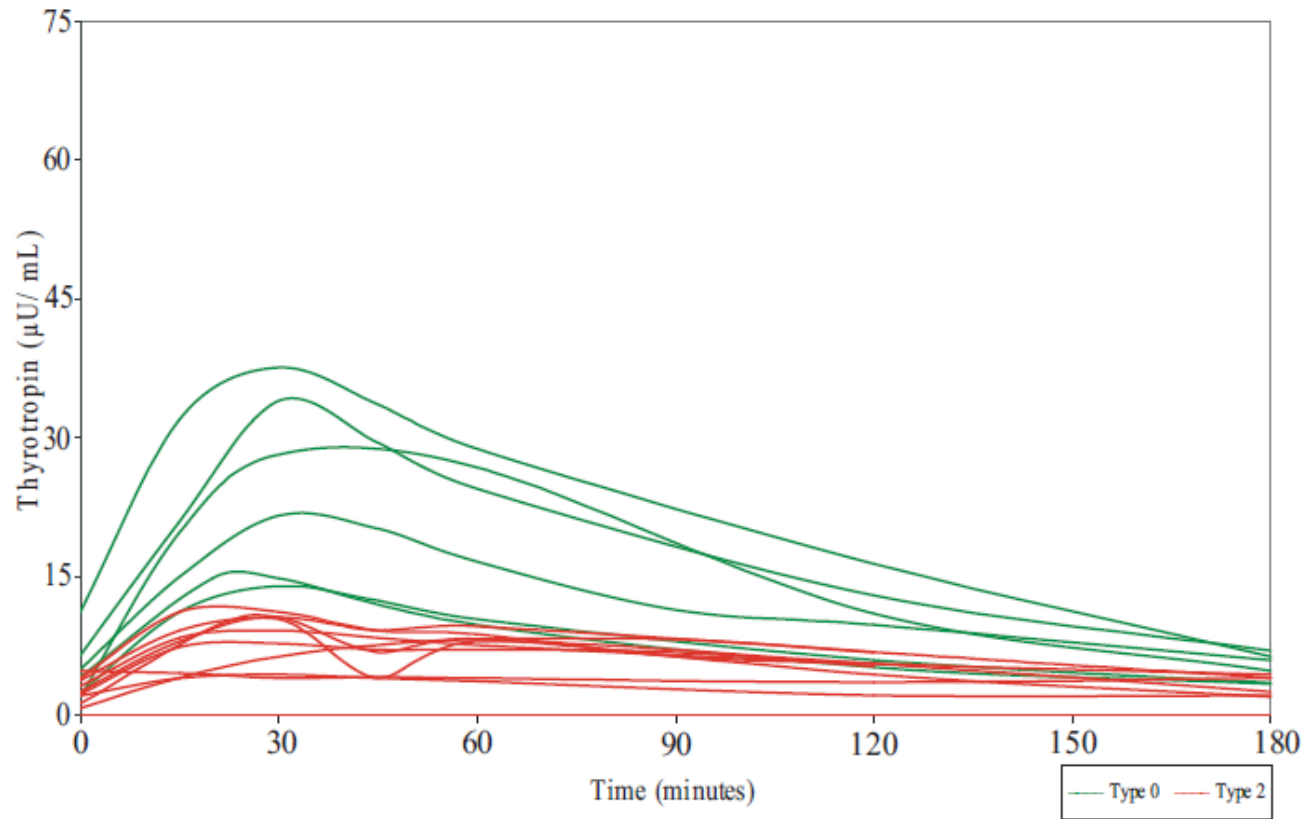
TRH-test

- Diagnose CHC obv FT4
- Waarom TRH-test



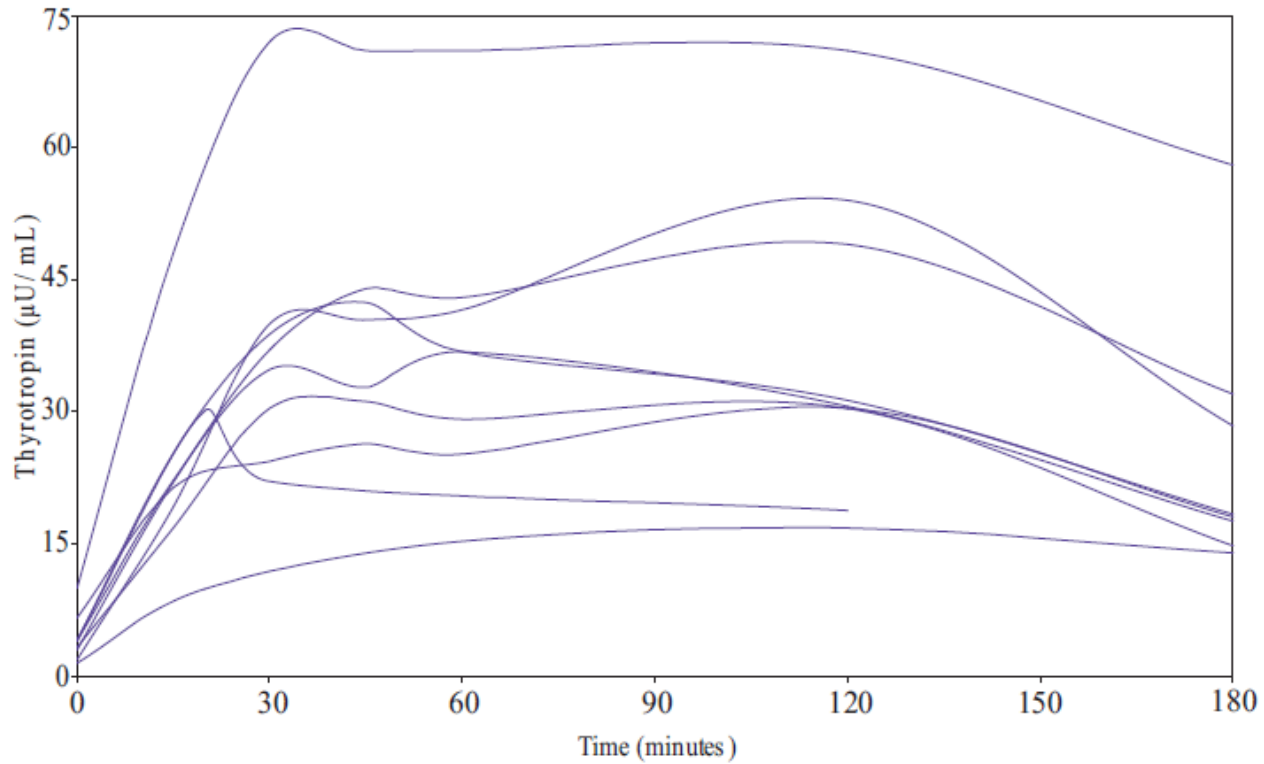
A

TRH-test: *type 0* & *type 2* responses

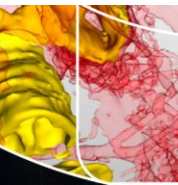
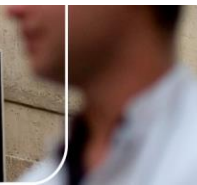


B

TRH-test: *type 3* response



Hypothalame oloop, past bij meest voorkomende hypofyse aanlegstoornis PSIS



Prematuren

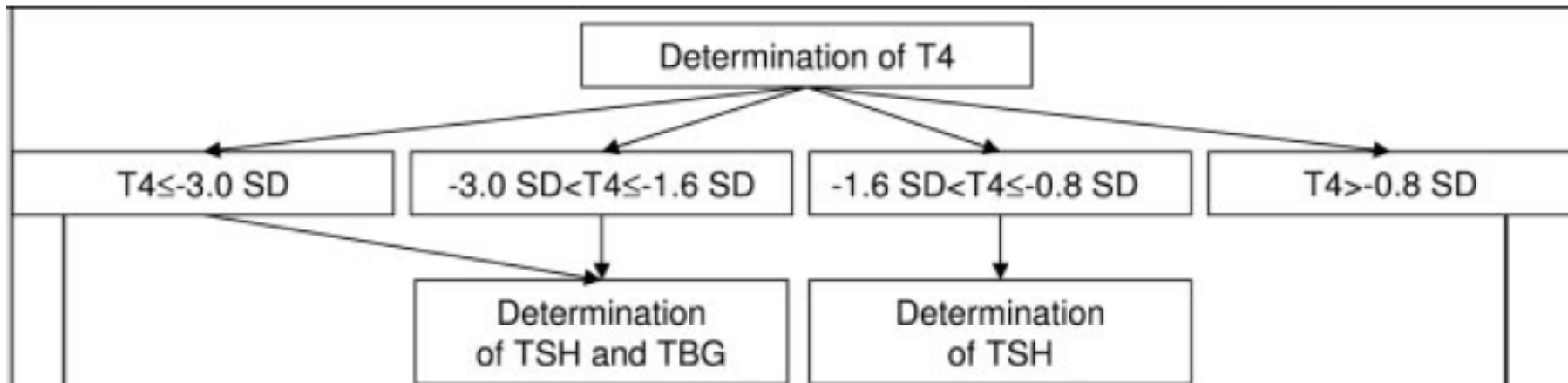
- Prematuren-regeling: geboortegewicht ≤ 2500 gram EN zwangerschapsduur ≤ 36 weken alleen **TSH-screening**
- ***geen* CH-C opgespoord**



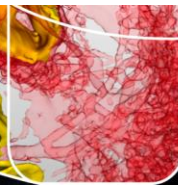
Casus 1

- Jongen, a terme geboren
- Ongecompliceerde graviditeit en partus
- Moeder geen schildklierziekte





- Dag 5: screenings-uitslag:
 - T4 39 nmol/l = -2.3 SD
 - TSH 108 mE/l
 - TBG 175,
 - T4/TBG ratio niet verlaagd
 - Thyreoidaal of centraal?



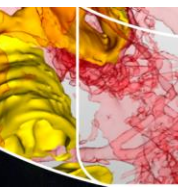
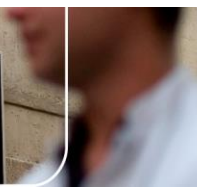
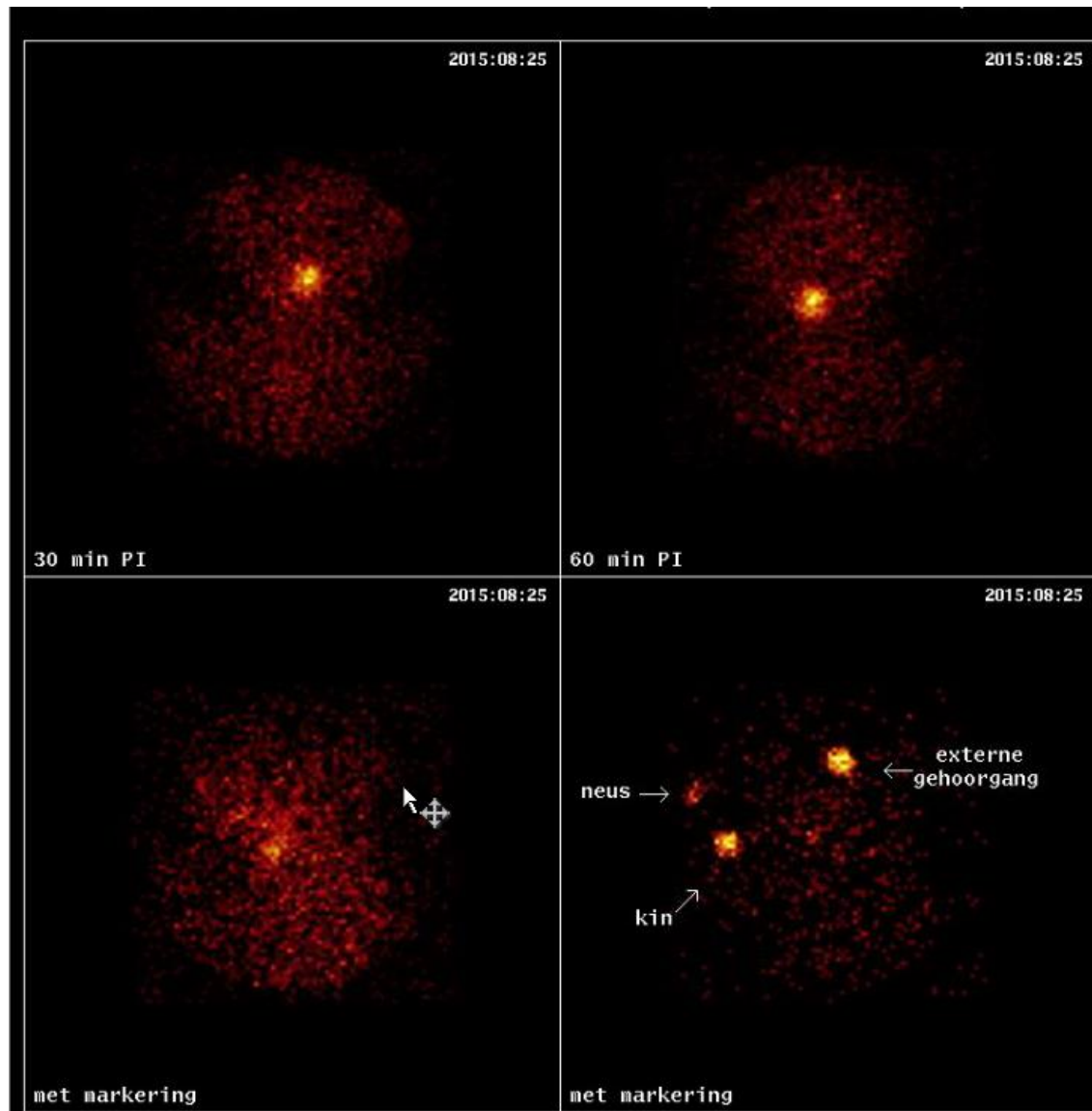
Differentiaal diagnose

- TSH duidelijk te hoog: thyreoidale CH
 - Aanlegstoornis
 - Dyshormogenese
- Veneus:
 - TSH > 100 mE/l, vrijT4 9 pmol/l (ref 12-30), Tg 2 pmol/l



123-jodide scan

Sublinguaal schildklierrudiment



Casus 2

- Meisje a terme geboren
- Afwijkende HP screening:
 - T4 -3.9 SD, TSH > 120, TBG 206



- Veneuze bloedafname
- TSH > 100 mE/l, FT4 5 pmol/l
- TG 763 pmol/l (sterk verhoogd)



Diagnose?

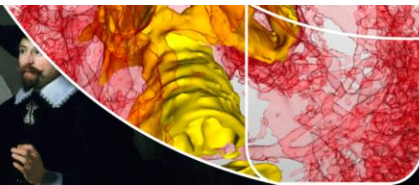


Table 1. Thyroid Ultrasound, Scintigraphy, and Serum Thyroglobulin Findings in Thyroid Dysgenesis, Dyshormonogenesis, and Some Forms of Transient CH

Defect	Thyroid Ultrasound	Thyroid Scintigraphy	Serum Thyroglobulin Concentration
Thyroid dysgenesis			
Apparent athyreosis	No thyroid tissue seen	No uptake	Detectable ($\geq 2 \mu\text{g/L}$)
True athyreosis	No thyroid tissue seen	No uptake	Undetectable
Ectopy	Either no thyroid tissue seen or ectopic tissue seen (especially if in a sublingual or perihyoid location)	Uptake into ectopic gland	Usually \uparrow but may be or \downarrow
Hypoplasia in situ	Small eutopic gland	Low level of uptake in a normally sited gland	N or \downarrow
Hemiagenesis	Hemithyroid	Hemithyroid	N
Dyshormonogenesis			
NIS/SCL5A5	Enlarged gland	Uptake absent or $\downarrow\downarrow$	\uparrow ←
Thyroid peroxidase, TPO	Enlarged gland	High level of uptake; positive perchlorate discharge test	$\uparrow\uparrow$
Dual oxidase 2, DUOX2/dual oxidase 2 maturation factor, DUOXA2	Enlarged gland	High level of uptake; positive perchlorate discharge test	\uparrow
Thyroglobulin, TG	Enlarged gland	Avid uptake; normal perchlorate discharge test	$\downarrow\downarrow$ or undetectable
Pendred syndrome, pendrin PDS/SCL26A4	Normal/enlarged gland	High level of uptake; positive perchlorate discharge test	\uparrow
Dehalogenase, IYD/DEHAL1	Enlarged gland	Avid uptake; normal perchlorate discharge test	\uparrow

ESPE guidelines 2015

Casus 3

- Jongen, a terme geboren
- Ongecompliceerde graviditeit/partus
- Postnataal hypoglykemieën

- Screening

dag 6: T4 46 nmol/l (-1.6 SD), TSH 1, lage T4/TBG ratio

dag 8: T4 38 nmol/l (-2.6 SD), TSH 1, lage ratio



Lichamelijk onderzoek

- Icterische zuigeling
- Ingedaalde testes, micropenis



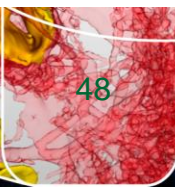
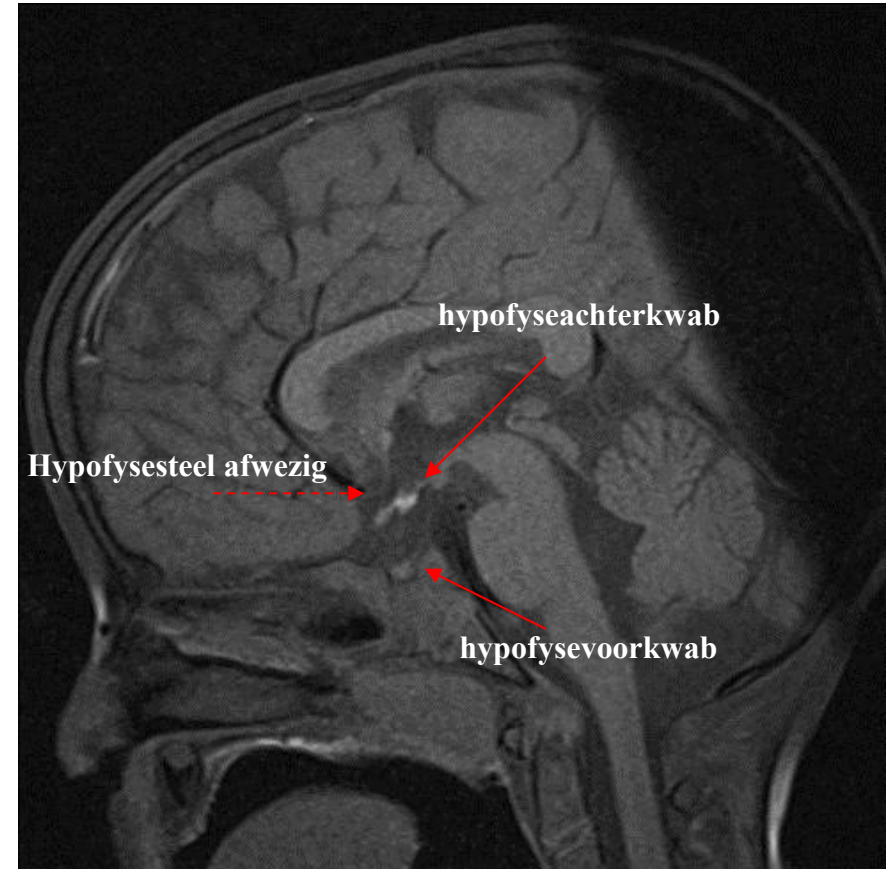
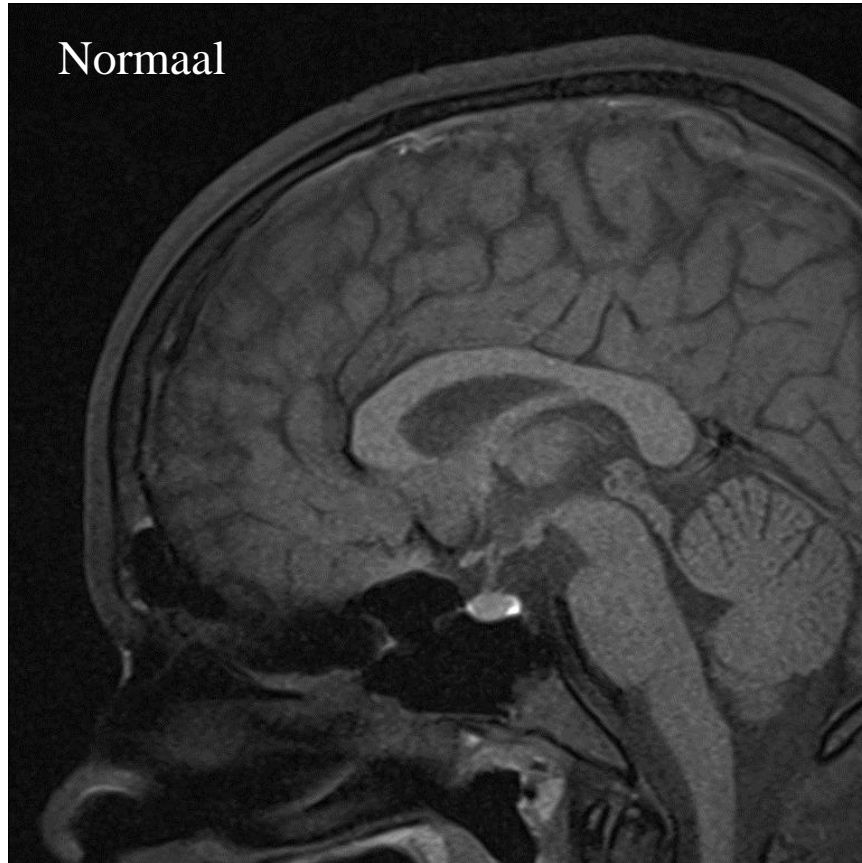
Aanvullend onderzoek

- Endocriene functie testen:
 - Schildklier-as: TRH test: type 3 respons ('hypothalaam)
 - Bijnier-as: CRH-test
 - Leeftijd 3 maanden: GnRH test, GH stimulatie testen



Diagnose:

Congenitaal hypofyse uitval bij hypofyse aanlegstoornis



Behandeling CHT

Therapie: Thyroxine

Behandeldoelen:

- Thyreoidaal – mik op “normaal” TSH

niet-strumagene CH: TSH binnen het LSRI

strumagene CH: TSH binnen het onderste tertiel van het LSRI (tussen 0,5 - 1,5 mE/l)



Behandeling CHC

Behandeldoel:

Centraal – mik op “normaal” FT4

Wat is referentie interval op deze neonatale leeftijd?

Individueel setpoint

Ref: FT4: 10-22 pmol/l ;

streefwaarde onder behandeling 15-22 (17 pmol/l)



Prognose

- Thyreoidaal:
 - veel beter dan vroeger
 - wel IQ deficit vergeleken met sibs
- Centraal:
 - ?



Treating patients not numbers: the benefit and burden of lowering TSH newborn screening cut-offs

Heiko Krude,¹ Oliver Blankenstein²

Arch Dis Child February 2011 Vol 96 No 2

