

RTH “Resistance Thyroid Hormone”

PREPARED BY: DR. FIDAA MAGHRABI

Supervised by: Dr. Ihab Halabi

Dr. Abdulmoein Al-Agha

History

- ▶ This is 4 years and 2 month old boy

Known of : - tiny PDA with left to right shunt based on echo

- sickle cell trait based on HB electrophoresis

- ▶ started to develop poor weight gain , palpitation and excessive sweating with irritability at the age of 1 year noticed by parents

No history of diarrhea .

No history of neck goiter or difficult swallowing , no cyanosis or SOB , no LN enlargement

No history of exophthalmos

No history of taking medication

No symptom of increased intracranial pressure

History

Antenatal hx : product of full-term , spontaneous vaginal delivery with birth Weight= 2.9 kg , mother was booked with normal us during pregnancy , pt discharge with mother in good condition .

Developmental hx : **gross motor** : Hops on one foot and Climbs well , **fine motor and vision** : Good pencil grip , **language and speech** : delayed (cannot count sequentially) **social** : Uses spoon and fork

Vaccination hx :up to 2 year

Nutritional hx :family food

No Past surgical hx

Family hx :his uncle did thyroidectomy at age of 14 years . Father complaining of tachycardia and insomnia Other siblings are healthy , no family hx of autoimmune disease

Examination

growth parameters :

Wt. 13 kg on 10th centile and ht 101 cm on the 26th centile
sleeping pulse 110 beat / minute with water hammer character

No tremors

No neck goiter or bruit

Chest :fair air entry

abdomen : soft, lax with no organomegaly

Heart : normal heart sounds with no murmurs

Neuro examination showed normal tone, power and reflexes

Differential diagnosis



Investigation ;

▶ CBC:

wbc = 9.6 , Hb= 12.9 , PLT= 292

▶ Hb electrophoresis :

Hb A= 52.5 % , Hb S= 35.1 % ,
Hb F = 1.9 %

▶ TFT :

TSH = 33.61 ↑ normal (0.27-4.2)

T3 = 18.86 ↑ normal (2.8 - 7)

T4 = 45.93 ↑ normal(12 - 22)

Differential diagnosis :

based on high TSH with high T4 :

What is the differential diagnosis



Differential diagnosis :

- ▶ 1- TSH secreting pituitary adenoma
- ▶ 2- resistance to thyroid hormone
- ▶ 3- Interfering antibodies to thyroid hormones
- ▶ 4- medications such as : Amiodarone , methadone or perphenazine .

Investigation ;

▶ Liver function test :

TP = 71g \l (64-82) , Albumin = 41g \l (40.2-47.6)

ALP=161 u\l (50-136) , AST =24 u\l (15-37) ,

ALT =19 u\l (12-78)

▶ Thyroid peroxidase antibody (TPO) = < 5

▶ Thyroid thyroglobulin antibody (TG) = < 10

▶ Neck U\lS = normal

▶ MRI brain : no pituitary adenoma .



Investigation ;

Blood sample sent for genetic study of patient ,
his parents , uncle and siblings

pedigree

Osama Kaabi Family Tree

Centaur Reference ranges

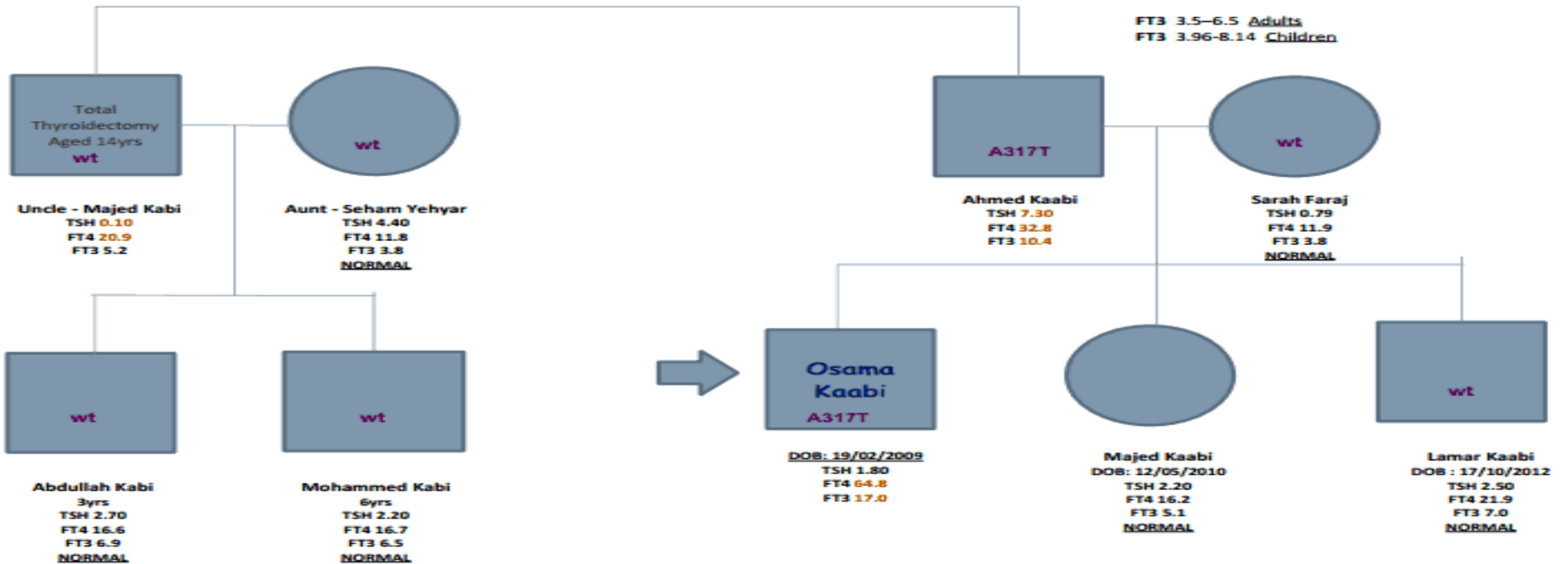
TSH 0.35–5.5

FT4 10–19.8

FT4 10.4–22.7 Under 1yrs of age

FT3 3.5–6.5 Adults

FT3 3.96–8.14 Children



Genetic study

- ▶ Our patient and his father has exhibited a mutation in the $THR\beta$ gene, A317T, due to a base pair substitution of an adenine for a threonine, which confirmed autosomal dominant inheritance .
- ▶ regarding his uncle , it seems that it was due to thyrotoxicosis as genetic analysis was normal and his thyroid function as well .



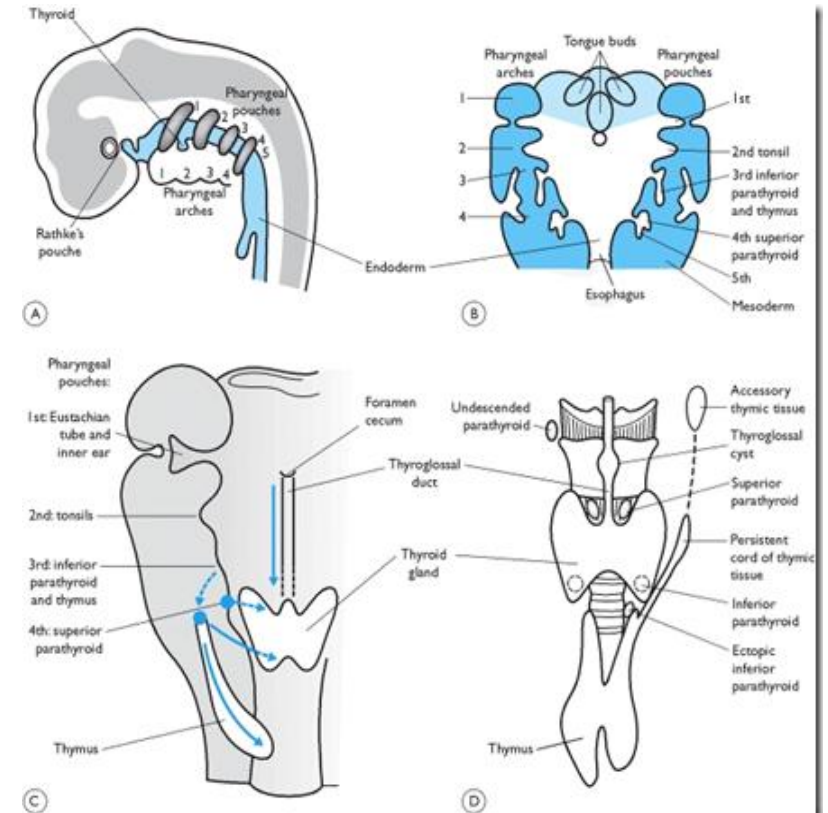
Diagnosis

Based on genetic analysis :

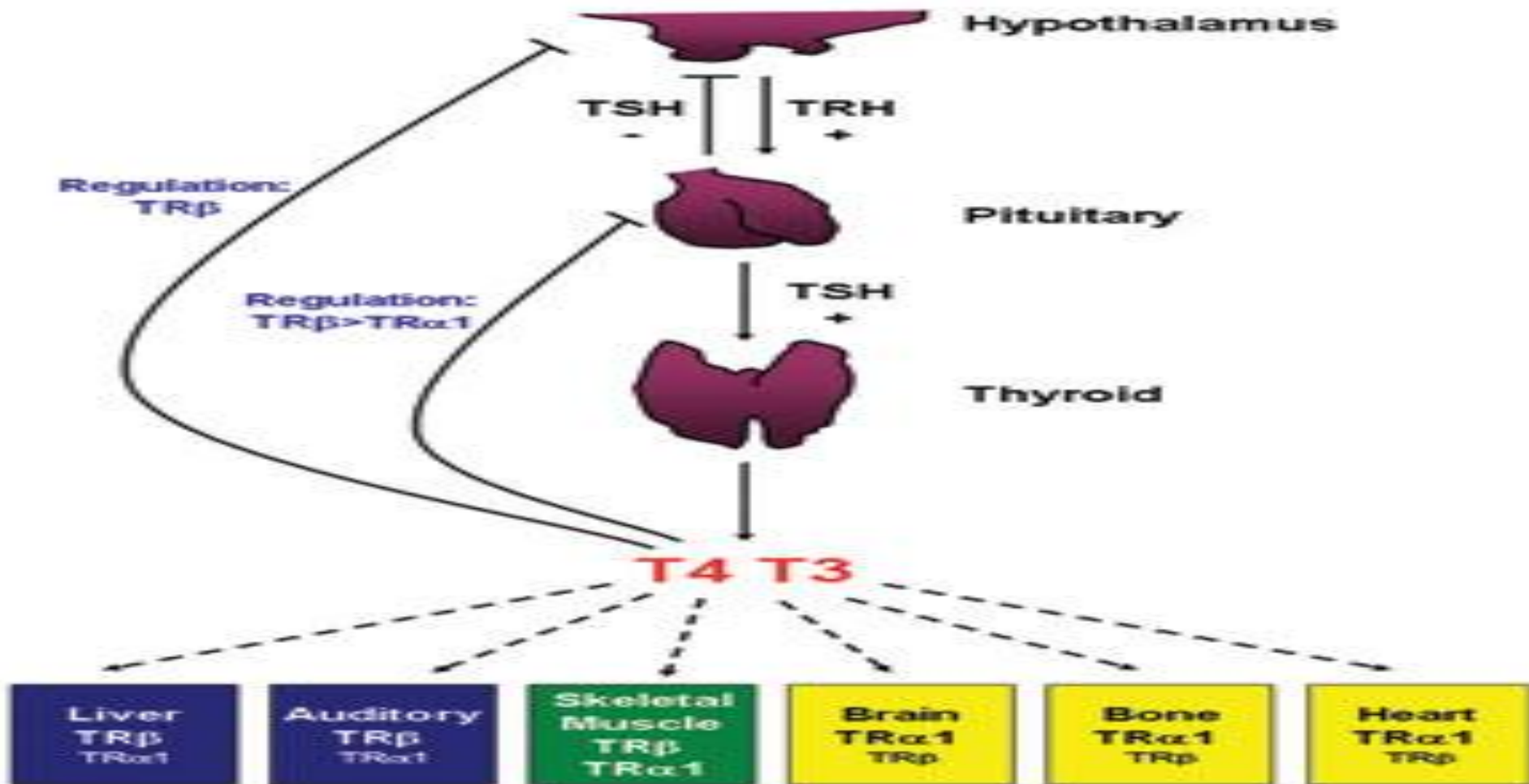
Resistance To Thyroid Hormone

Thyroid embryology

- ▶ The thyroid gland is a down growth from the pharyngeal endoderm of the developing tongue , and descends to its definitive position in the anterior lower neck by the end of the first trimester
- ▶ Bilobed shape is recognized by 7 week of gestational age , and characteristic thyroid follicle cell and colloid formation is seen by 10 week of gestational age , T3 and T4 secretion occur from 12 wk. of gestation .
- ▶ Peripheral metabolism of thyroid hormones matures in the third trimester .

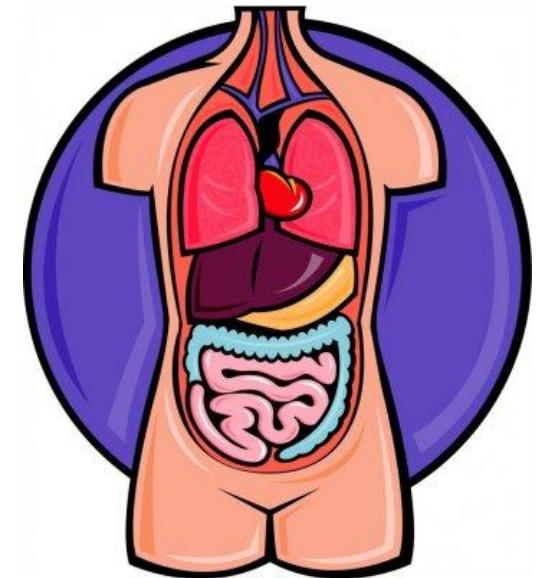


Hypothalamic – pituitary – thyroid axis

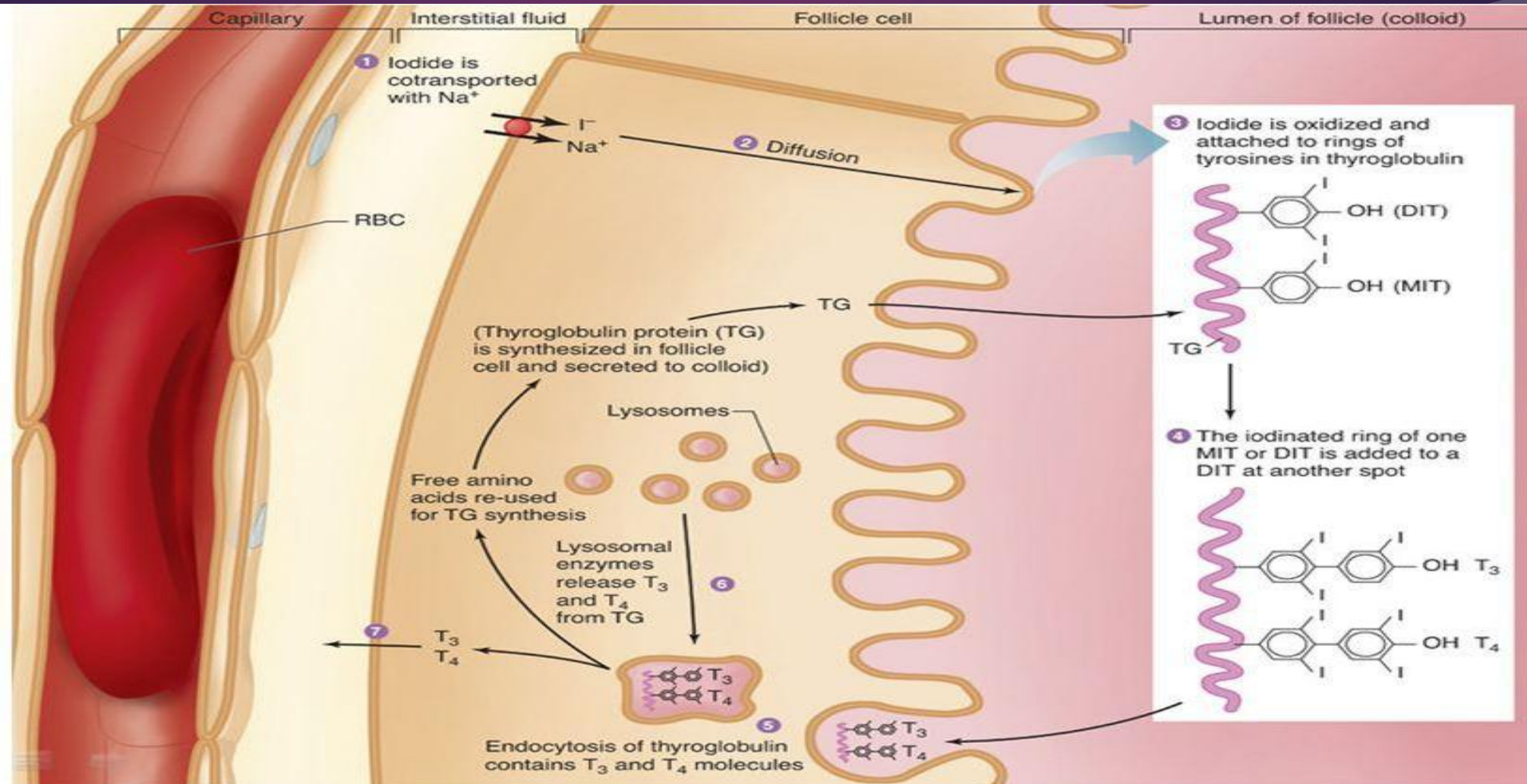


Important of thyroid hormone

- ▶ nervous system : required for myelination of neurons and development of the brain .
- ▶ cardiovascular system : to increase cardiac output, heart rate and contractility.
- ▶ increase basal metabolic rate and regulate long bone growth
- ▶ Alimentary system,
- ▶ Reproductive system, respiratory system ,

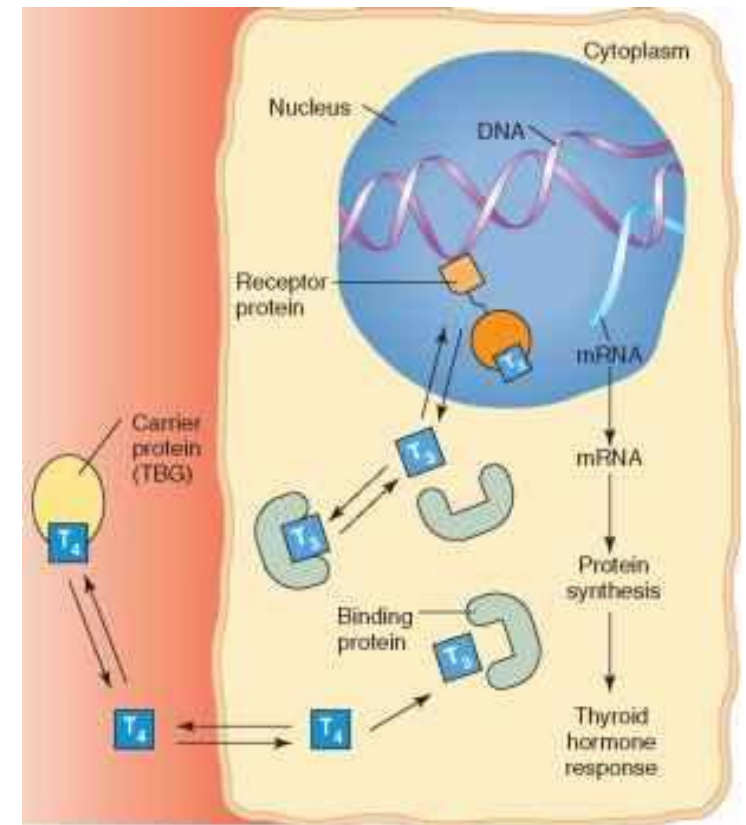


Thyroid hormones production



Thyroid receptors

- ▶ Thyroid hormone receptors TR α TR β located in cell nuclei , mediate the action of thyroid hormone by positive and negative regulation of TH responsive genes .
- ▶ TR β and TR α (located on chromosomes 17 and 3 respectively) most often coexist in the same tissue , Although the genes coding for these isoforms are generally differentiall expressed .
- ▶ three main receptor isoforms (TR α 1,TR β 1,TR β 2) ,
 - 1- TR α 1: mainly located in central nervous system, myocardium and skeletal muscle
 - 2- TR β 1: predominant in liver and kidney
 - 3- TR β 2 : highly expressed in the pituitary and hypothalamus



Mechanism of thyroxine action



Resistance to thyroid hormone (RTH)

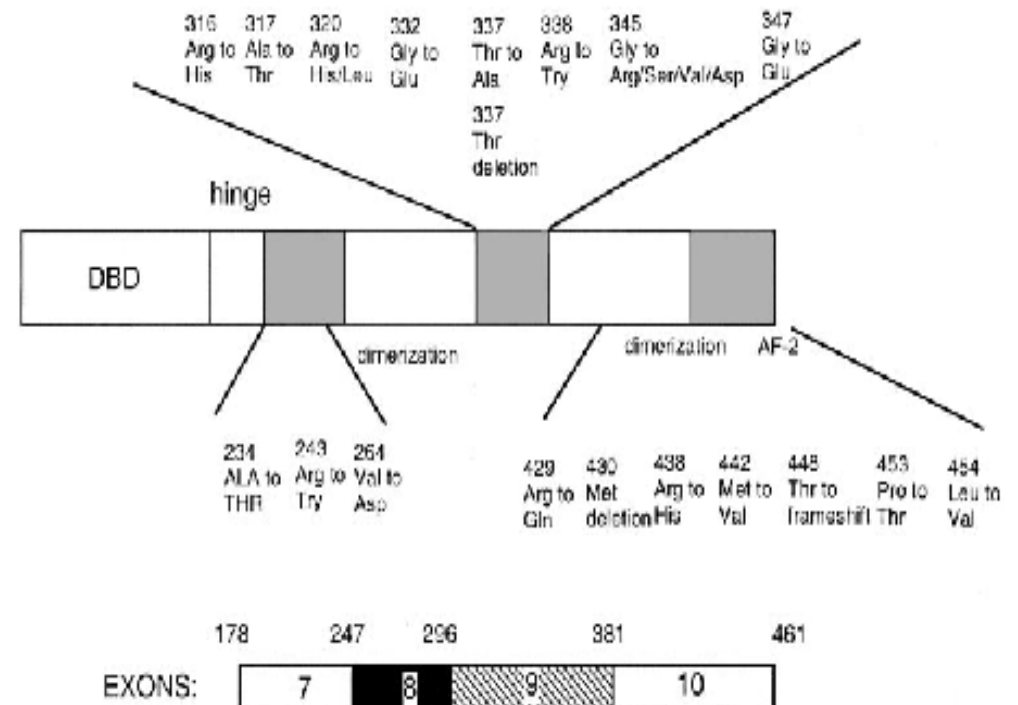
▶ Resistance to thyroid hormone ;

Is an inherited syndrome of reduced tissue responsiveness to thyroid hormone

- ▶ Usually inherited in an autosomal dominant trait .
- ▶ First case reported in 1967 , with symptoms of hypothyroidism and goiter with delayed bone age and deafness .
- ▶ Molecular basis for RTH has been reported in 166 families .
- ▶ The incidence probably 1 case per 40,000 live newborns .
- ▶ This disease is characteristically demonstrate elevated (FT3) and (FT4)level with no suppressed or normal serum (TSH)

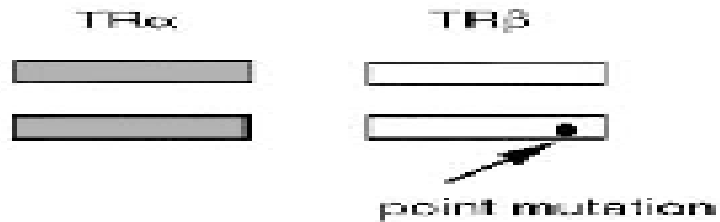
Causes of resistance

- ▶ Point mutation in one allele of the TR β gene
Seventy-six different point mutation was reported (most common)
- ▶ deletion mutation : 8 reported cases
- ▶ insertion mutation : 7 reported cases
- ▶ only one case has been described that is not due to a mutation in TR α or TR β , it is thought to be due to a defect in specific cofactors essential in mediating thyroid hormone action at the nuclear level



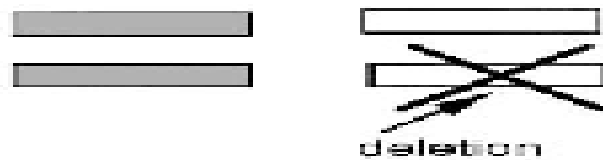
Dominant negative interaction

TR β MUTANT HETEROZYGOTE



RTH

TR β DELETION HETEROZYGOTE



No disease

TR β DELETION HOMOZYGOTE



Severe RTH

Clinical manifestations

- ▶ Clinical presentation of RTH is highly variable and clinical findings are suggestive of either hyperthyroidism , hypothyroidism or euthyroidism .
- ▶ Clinical and laboratory indicators differ even within the same family
- ▶ The serum free T4 levels can range from slightly above normal to manifold the upper limit of normal and it reflect resistance to the negative feedback by TH in the pituitary and hypothalamus .
- ▶ Peripheral tissues are dependent on the pituitary gland for the supply of TH

Hypothyroidism

IF a particular tissues were more resistant than the thyrotrophs (TSH cells) [due to differential expression of tissue – specific cofactors or the mutant TR β itself] that tissue would be TH deprived

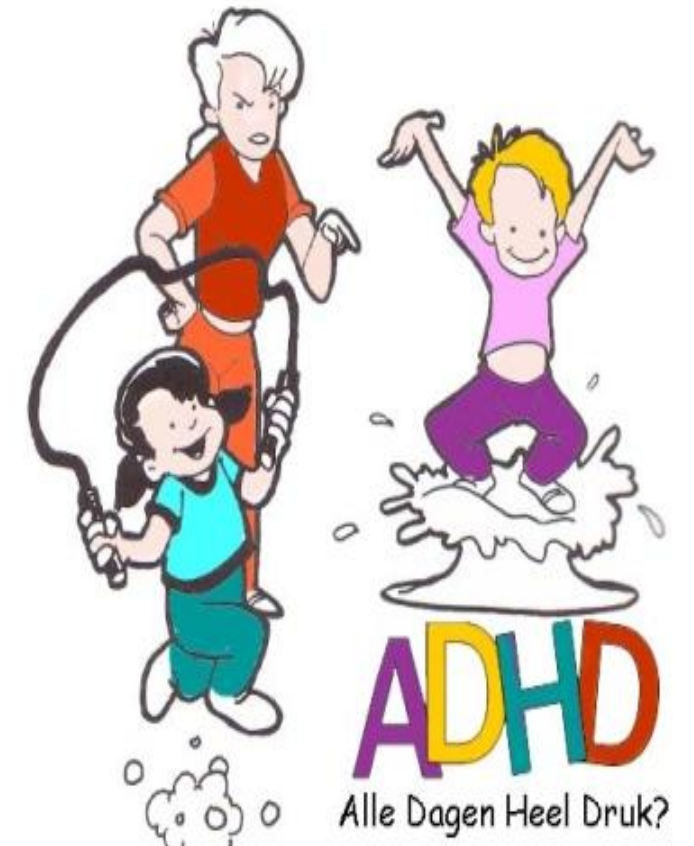
Manifested by :

- ▶ Growth retardation , impaired cognitive ability , Developmental Delay , deafness and Low IQ .



Hyperthyroidism

- ▶ If tissue subjected to TH excess and not as resistant as the thyrotrophs , that tissue would be hyperthyroidism .
- ▶ Manifested by :
Tachycardia , advance bone age , hyperactivity , failure to gain weight , insomnia , goiter , hearing loss and Attention Deficit Hyperactivity Disorder (ADHD)
- ▶ Some individuals may have mixed hypothyroid and hyperthyroid symptoms



Euthyroidism

- ▶ IF the peripheral tissues were as resistance as the pituitary the net effect would be overall euthyroidism .
- ▶ In this case the thyroid gland is able to compensate for the mutant TR β by increasing TH production .



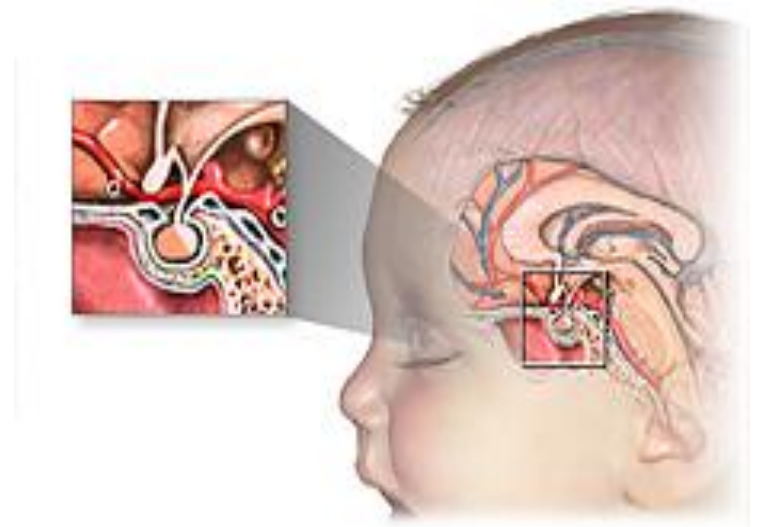
Classification of RTH

1- pituitary or central resistance to thyroid hormone (PRTT)

The patient appeared clinically thyrotoxicosis .

2- generalized resistance to thyroid hormone (GRTH)

The patient appeared clinically euthyroid or hypothyroidism.



Investigation for RTH

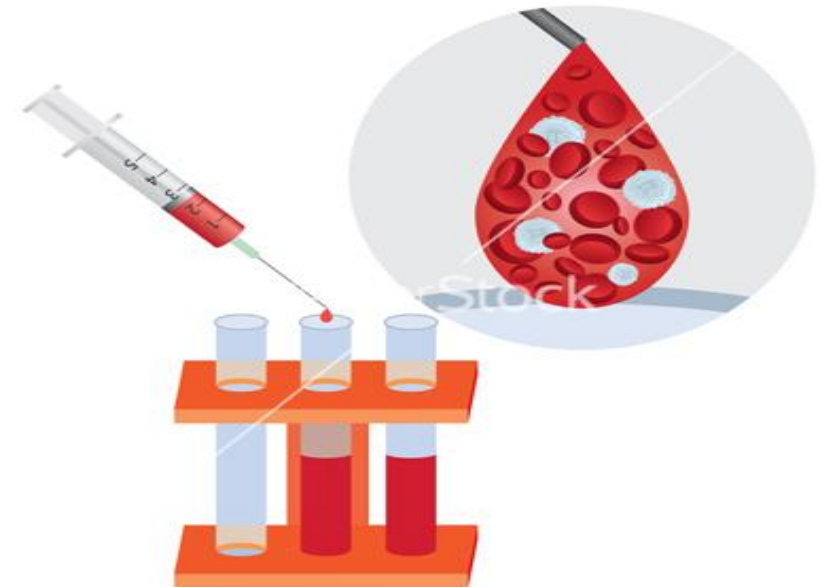
1- thyroid function test: This usually shows high levels of T3 and T4 with normal or slightly high TSH .

2- blood test called 'alpha subunit' and (MRI) scan of the brain to exclude TSH-secreting pituitary adenoma .

3- TRH test

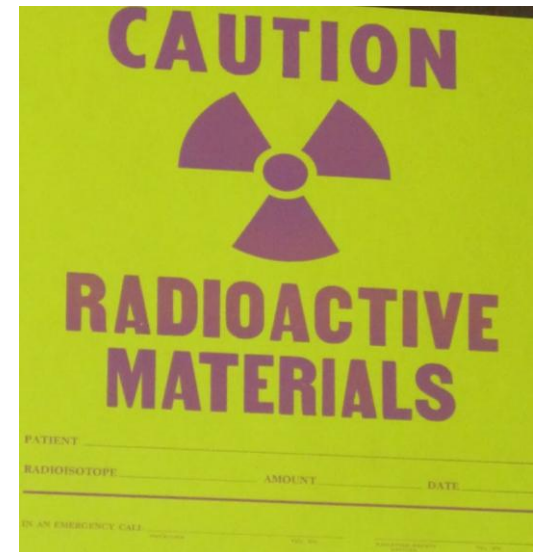
4 - genetic testing (blood sample)

5 - family members TFT and genetic study



Management Review

- ▶ The majority of cases are asymptomatic except for a goiter and abnormal laboratory test result .
- ▶ These patients have been misdiagnosed as having hyperthyroidism and were given anti-thyroid medications , ablation with sodium iodide I 131 or thyroidectomy . Their physicians thereafter become alarmed because of seeming recurrence of disease and required higher than usual doses of levothyroxine or additional doses of I 131.



Management Review

Chronology of Inappropriate Treatment (Surgery, ¹³¹I, Antithyroid Drugs) of Subjects with RTH in Relation to Number of Published Cases

Period (years)^b	Treated^a		Number Published	
	Subjects	Families	Subjects	Families
Before 1967	17	15	2	1
1968 to 1977	40	27	18	6
1978 to 1987	53	41	126	42
1988 to present	8 ^c	7 ^c	150	49
Total	118	90	296	98

a Treatment in almost all cases was given before recognition of RTH, antedating their publication. This explains the apparent discrepancy between the number of cases who received treatment and the number of cases published, most notably until 1977

b When year of treatment was not available, or could not be deduced from available information, the year of publication was used. This occurred in 16 of 118 treatments.

c The year of treatment was not given in 7 of the 8 subjects belonging to 6 of the 7 families

Reprinted from Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. *Endocr Rev.* 1993;14:348-399.

Management Review



- ▶ The ideal way to treat patient who have RTH would be to reverse the dominant negative effect of the mutant TR β .Unfortunately this is not possible at present
- ▶ So we go to treat hypothyroidism with TH and reducing symptoms consistent with hyperthyroidism .
- ▶ The methods include :
 - 1- decreasing the symptoms through β -adrenergic blockade
 - 2- partially suppressing TSH in order to decrease TH
 - 3- use of TH analogues which have a differential effect on the pituitary and the peripheral tissues.

Management Review



► **B-Blockers :**

- Palpitations and tachycardia are common features of spontaneous hyperthyroidism which are best management by β -blockers .
- Propranolol have the added effect of inhibiting the conversion of T4 to T3 .
- Although this effect is desirable in treating spontaneous hyperthyroidism it is counterproductive in patient with resistance receptors .
- atenolol preferred to use it in treating tachycardia in TH-resistant patients because it does not block the conversion of T4 to T3 , and the dose is titrated to the heart rate

Management Review



► Dopaminergic drugs and Somatostatin :

- A logical approach to management of the hyperthyroid symptoms of RTH is the use of agents that suppress TSH secretion .
- Glucocorticoids : effective in reducing the serum TSH concentration but have unacceptable side effect
- Dopaminergic agent such as bromocriptine ; have been effective in reducing the serum TSH concentration but lose their effectiveness when taken for prolonged periods .
- Somatostatin analogue SMS201-995 :limited use because of their side effects and was found to be weaker and more transient in 3 patients with RTH , and may cause a paradoxical increase in TSH concentrations in some patients with RTH also, need frequent daily injections .

Management Review



► Triiodothyroacetic Acid (TRIAC) ;

- Is a TH analogue with low in vivo hormonal potency but high affinity for the TR . The binding affinity of TRIAC is almost 3 times that of T3 for normal TR β ,whereas it has similar affinity for TR α .



Management Review

■ Table 2

Effect of TRIAC on Thyroid Function Tests and Peripheral Tissue Markers of Thyroid Hormone Action in Subjects With Resistance to Thyroid Hormone

Change From Baseline (%)

Subject, Age, Sex	Dose, mg (weeks)	Serum Thyroid Function				Peripheral Tissue Effects				
		TSH basal	TSH peak*	FT ₄	FT ₃	Pulse rate	PEP/ LVET	Cholesterol levels	Bone	SHBG
17y F ²⁶	1.4 (3)	-46	ND	-59	-28	0	-7	ND	ND	ND
47y F ²²	2.1 (6)	-50	-14	-44	-32	+1.0	0	ND	ND	ND
47y F ²²	2.1(16)	-40	-50	-37	-42	-15	+30	+38	ND	ND
11y F ³⁰	2.1 (88)	-80	-59	-42	-42	-95	ND	0	—	-43
3.5y M ³¹	1-1.75 (96)	-55		-48	ND	-24	ND	ND	0	-8.0
37y F ³²	2.8 (10)	-90	-91	-32	ND	0	0	ND	ND	-50
42y M ³³	2.8 (6)	-75	-97	-19	ND	0	0	ND	ND	0

LVET, left ventricular ejection time; ND, no data; PEP, preejection period; SHBG, sex hormone binding globulin; TRIAC, triiodothyroacetic acid.

*Peak, after thyrotropin-releasing hormone.

Management Review



► T3 and psychological abnormality :

- from 48% to 73% of children with RTH have attention deficit hyperactivity disorder (ADHD)
- observation of pt. with RTH has suggested that treatment with TH may improve the symptoms of ADHD , whereas methylphenidate may not be helpful .

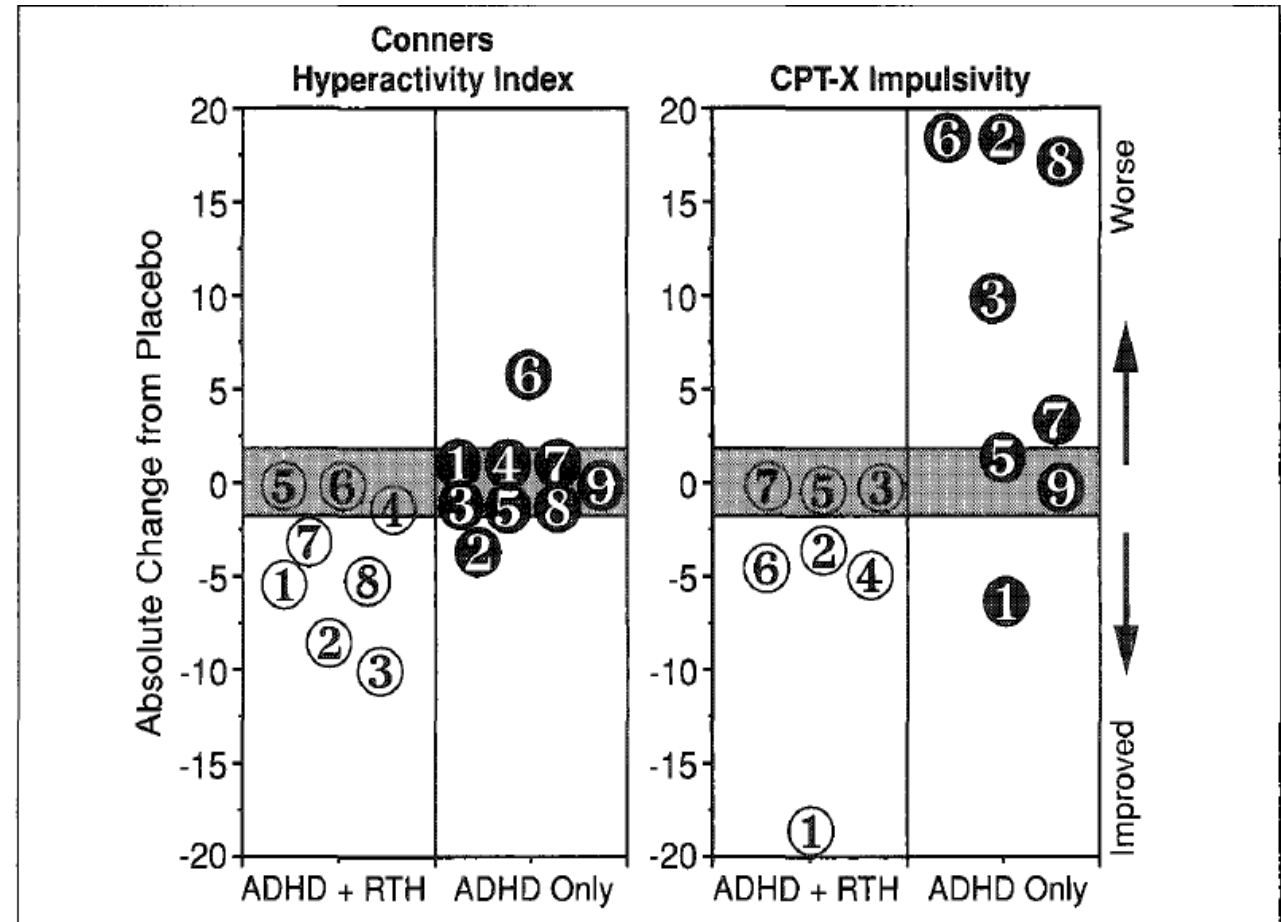
A prospective , randomized , double-blind , placebo-controlled study was conducted to evaluate the effect of L-T3 on the behavior of 8 children who had ADHD with RTH and 9 children who had ADHD and normal thyroid function .

Parent and teacher ratings of hyperactivity (conners scale) and computerized continuous performance test (CPT) were the objective measures of hyperactivity , attention and impulsivity

Management Review

► Conclusion:

In children with ADHD and RTH which treated with L-T3 in supraphysiologic doses may be beneficial in reducing hyperactivity and impulsivity .



Management Review



► T3 and growth :

Growth retardation and short stature attributed to functional deficiency of TH and common with RTH .

-study conduct 103 persons from 42 families at the national institutes of health . Data showed that 9 (16%) of 57 children and 9 (20%) of 45 adults also had short stature .

Delayed bone maturation is also common in RTH .

-the NIH study showed that 10 (29%) of 35 persons had delayed bone age .

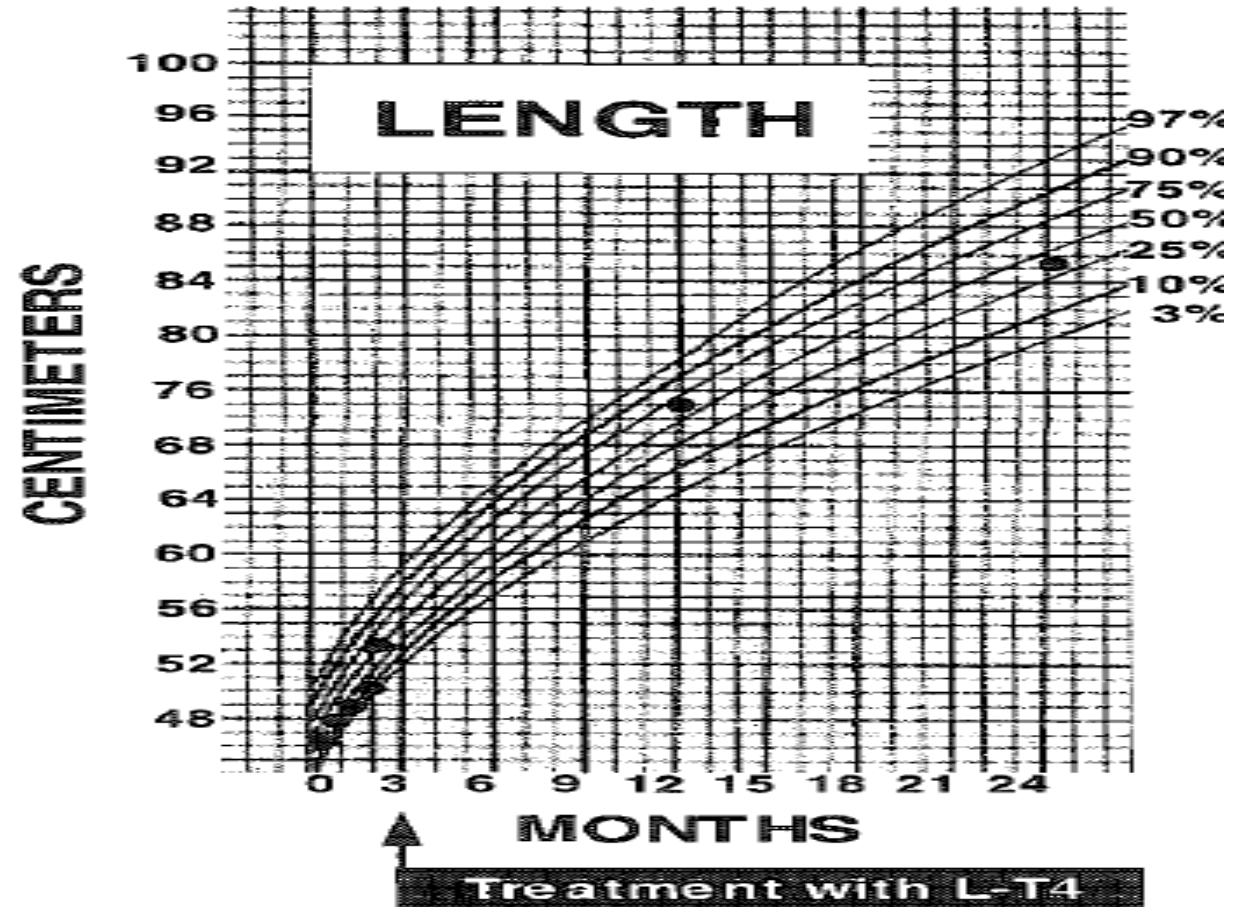
-Short stature and delayed bone age did not seem to be related to the location of the mutation in the TR β gene .



Management Review

► Conclusion :

Lowering thyroid hormone levels reduced the rate of bone development and linear growth .
Treatment with thyroid hormone had the opposite effect .





▶ Back To Our Case

Management :

neomercazole with Inderal started as trial



Follow up

► PT following on the clinic :

Showed slightly improving in tachycardia but still there was same symptoms with high TSH and T4 .

TSH= 34.90 ↑ normal (0.27 – 4.2)

T3= 16.62 ↑ normal (2.8 - 7)

T4 = 52.19 ↑ normal (12 – 22)



Mechanism of action

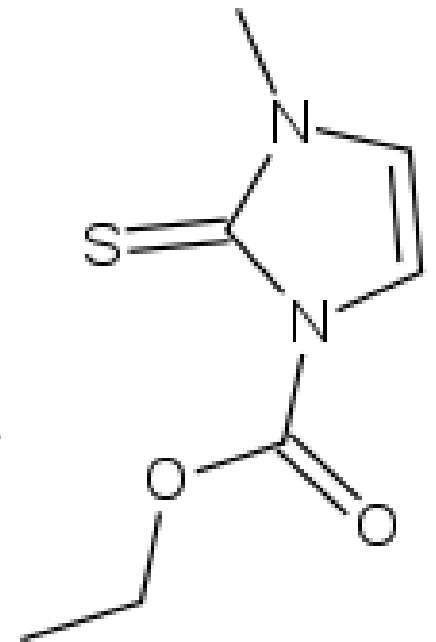
- Propranolol (Inderal) :

non selective β -blocker , it is effective in decreasing tachycardia but have the added effect of inhibiting the conversion of T4 to T3 which is count productive in RTH

- Carbimazole (Neomercazole) :

prevents the thyroid peroxidase enzyme from coupling and iodinating the tyrosine binds with thyroglobulin , and reducing the production of the thyroid hormones (T3 and T4) .

In RTH this mechanism stimulate pituitary to increase secretion of TSH to increase thyroid hormone and cause thyrotrophs hyperplasia.



Follow up

- ▶ So , the medication stopped

Follow up

as TRIAC is not available, prednisolone was decided to be started every other day in order to get suppression of TSH and to minimise the side effects of corticosteroid therapy.

*** Steroid 2mg \ Kg alternative day with atenolol 2mg \ Kg started**



Follow up

On follow up :

- ▶ Symptoms showed impressive improvement

no tachycardia (HR = 85)

no irritability or sweating

- ▶ Growth parameters improving and appropriate for patient age.



Growth parameters

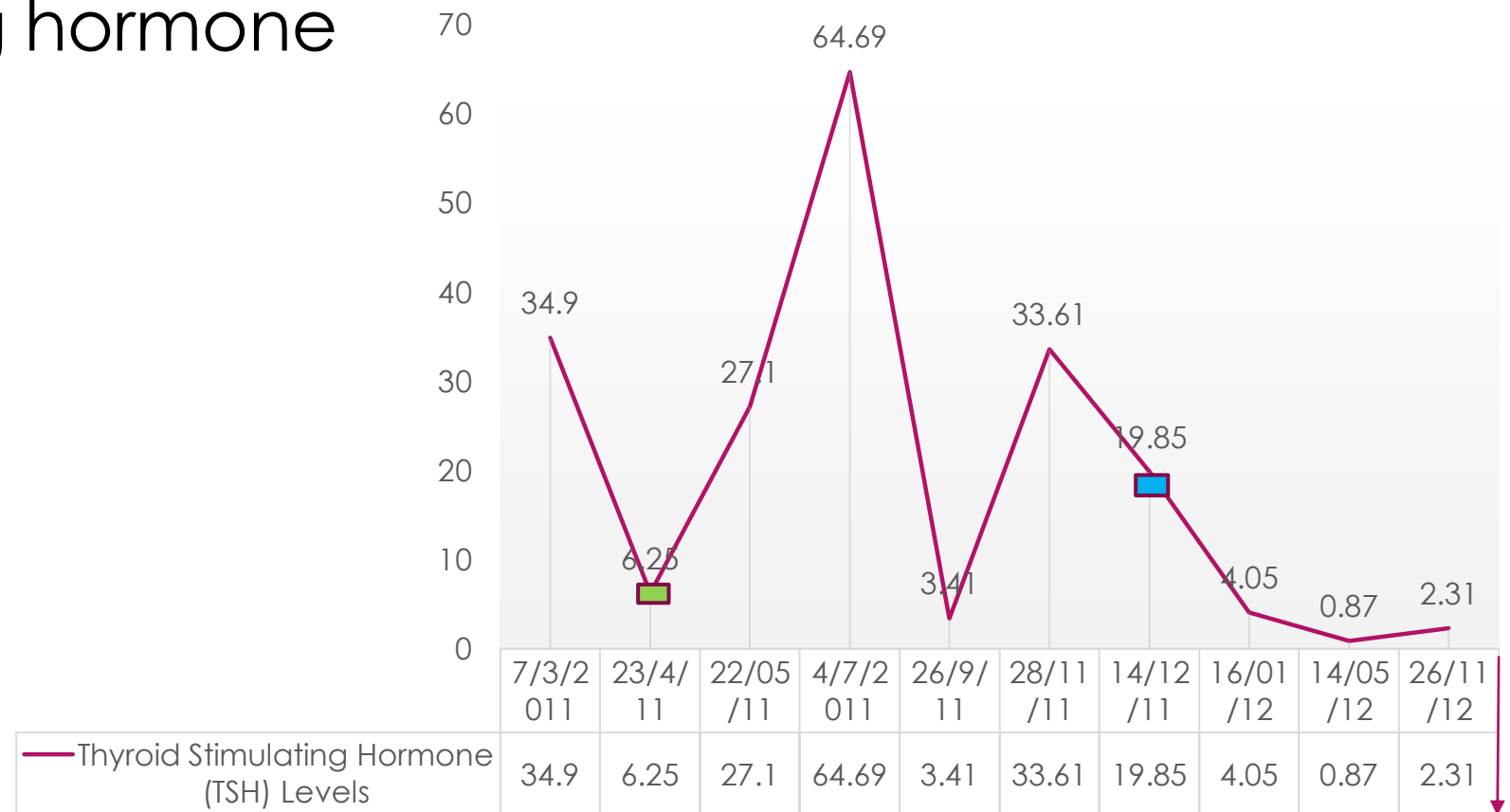
	2m	4m	13m	21m	28m	36m	4 yr	4 yr + 2m
Ht Z-score	-4	-4	-1.9	-0.1	-0.1	-1	-0.4	-0.3
Wt Z-score	-2	-1.9	-2.1	-0.8	-0.7	-1.2	-1.9	-2

Thyroid Function Test

Thyroid stimulating hormone

■ Date of starting of Neomercazole

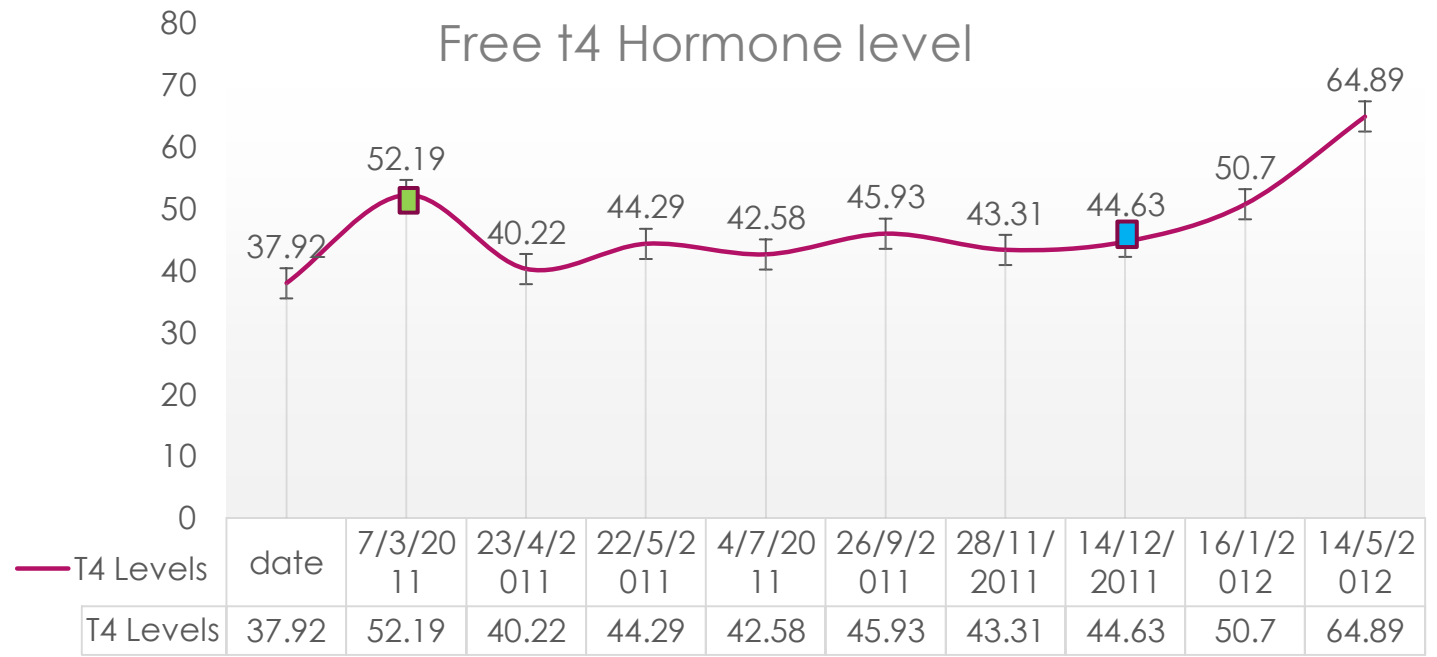
■ Date of starting of Prednisolone



Thyroid Function Test

■ Date of starting of Neomercazole

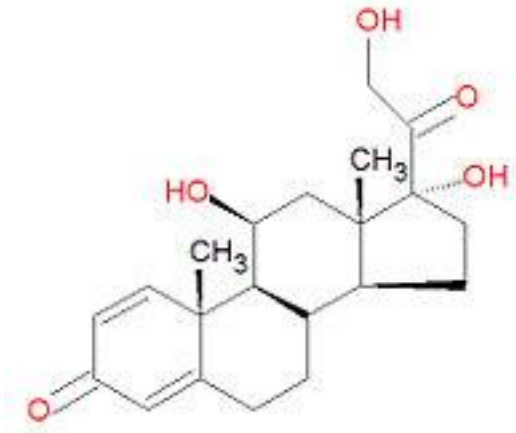
■ Date of starting of Prednisolone



Mechanism of Action

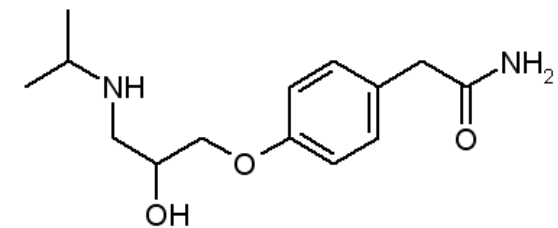
- Prednisolone :

act as primary mechanism for lower TSH secretion from the pituitary , through inhibition of TRH in the hypothalamus by decrease TRH mRNA levels in the hypothalamus .



- Atenolol :

is a selective β_1 receptor antagonist , preferred to use it in treating tachycardia in TH-resistant patients because it does not block the conversion of T4 to T3 .



Follow up

- ▶ After 18 month of compliance on steroid as alternative day no side effects appear :

Blood pressure within normal 105 - 95\ 65– 60

No symptoms of hyperglycemia , last fasting blood sugar = 4.7 on 2013

CA= 2.5 , total 25 hydroxyl vitamin D was 76.3 nmol/l (50-80) as he was on 1000 lu of vitamin D

Dexa scan done :

Z- score = -1.0 (which denotes osteopenia)

Studies



Resistance to thyroid hormone in a Turkish child with A317T mutation in thyroid beta receptor gene .

Turkish journal of pediatric , 2008 .

► Case report from Istanbul university hospital in turkey .

23 month Turkish female , product of FT , SVD , birth weight = 3.5920kg , she was euthyroid with high T4 ,T3 and normal TSH

Examination was normal

Her mother had goiter , started on anti-thyroid medication for 3 years and during pregnancy due to hyperthyroidism

MRI done to exclude pituitary adenoma , normal

Genetic analysis done for patient and mother and reflect mutation in TR β A317T , due to substitution of adenine to guanine

Familial partial target organ resistance to thyroid hormones.

Elewaut A; Mussche M; Vermeulen A

J Clin Endocrinol Metab; 1976 Sep; 43(3):575-81. PubMed ID: 60346

Case report :

- ▶ A 30-year old woman with a history of recurrent goiter after two partial thyroidectomies , presented with tachycardia, nervousness and a fine tremor
- ▶ T3 , T4 and binding protein were normal , and a very high serum thyrotropin (TSH), During follow-up T4 and T3 increased while TSH decreased , TRH test done was normal pituitary response .
- ▶ All the relatives studied (father, sister, three children) had elevated T4 levels with normal basal TSH values
- ▶ Treated by : 60 mg prednisolone daily resulted in a blunting of the response to TRH.

50 mg T3 daily for 1 month resulted in a fall in serum TSH from 98 to 5

20 mg carbimazole daily for 3 weeks resulted in a decrease in serum T4 levels with increase of serum TSH

Pt revealed much laboratory and symptoms improvement and diagnosis of RTH is established by genetic study

Thyroid hormone resistance detected by routine neonatal screening

lea maria maciel , patricia kunzle Ribeiro magaihaes
j .Brazilian endocrinology metabolism . 2010

- ▶ Brazilian patient with resistance to thyroid hormone system (RTH) , was born at term by normal vaginal delivery with 2.920 kg and height 45 cm .
- ▶ Neonatal screen on 5th day showed high TSH , in confirmatory test serum TSH normal T4 and T3 was high . Direct sequencing of beta thyroid hormone receptor gene revealed mutation c.1357C>A (p453T) .
- ▶ Family study demonstrated the presence of RTH in his 1-year and 3 month old **sister** , in his 35 year – old **father** and in his 68 year-old **paternal grandfather** . All of them had goiter and only his father diagnosed as hyperthyroidism .

▶ In conclusion :

this case report shows that clinical evaluation and judicious interpretation of total T4 and free T4 concentrations in a newborn recalled due to slightly alerted neonatal TSH can contribute to the diagnosis of RTH .

Take Home Messages

- ▶ Good history taking leads to proper diagnosis
- ▶ Physician should be aware about abnormal TSH and T4 results , resistant to thyroid hormone and pituitary adenoma should be in the differential



References :

- ▶ 1. Elewaut, A., M. Mussche, and A. Vermeulen, *Familial partial target organ resistance to thyroid hormones*. J Clin Endocrinol Metab, 1976. **43**(3): p. 575-81. 2. Maciel, L.M. and P.K. Magalhaes, *Thyroid hormone resistance detected by routine neonatal screening*. Arq Bras Endocrinol Metabol, 2010. **54**(8): p. 723-7.
- ▶ 2. Maciel, L.M. and P.K. Magalhaes, *Thyroid hormone resistance detected by routine neonatal screening*. Arq Bras Endocrinol Metabol, 2010. **54**(8): p. 723-7.
- ▶ 3. Poyrazoglu, S., et al., *Resistance to thyroid hormone in a Turkish child with A317T mutation in the thyroid hormone receptor-beta gene*. Turk J Pediatr, 2008. **50**(6): p. 577-80.
- ▶ 4. Weiss, R.E. and S. Refetoff, *Treatment of resistance to thyroid hormone--primum non nocere*. J Clin Endocrinol Metab, 1999. **84**(2): p. 401-4.

References :

- ▶ 4. John CD, Christian HC, Morris JF, Flower RJ, Solito E, Buckingham JC. Kinase-Dependent Regulation of the Secretion of Thyrotrophin and Luteinizing Hormone by Glucocorticoids and Annexin 1 Peptides. *J.Neuroendocrinol.* 2003;15(10):946–57. [PubMed]
- ▶ 5. Cintra A, Fuxe K, Wikstrom AC, Visser T, Gustafsson JA. Evidence for Thyrotropin-Releasing Hormone and Glucocorticoid Receptor-Immunoreactive Neurons in Various Preoptic and Hypothalamic Nuclei of the Male Rat. *Brain Res.* 1990 Jan 1;506(1):139–44. [PubMed]
- ▶ 6. Alkemade A, Unmehopa UA, Wiersinga WM, Swaab DF, Fliers E. Glucocorticoids Decrease Thyrotropin-Releasing Hormone Messenger Ribonucleic Acid Expression in the Paraventricular Nucleus of the Human Hypothalamus. *J.Clin.Endocrinol.Metab.* 2005;90(1):323–7. [PubMed]

Thank You

