Thyreopathy in childhood and puberty

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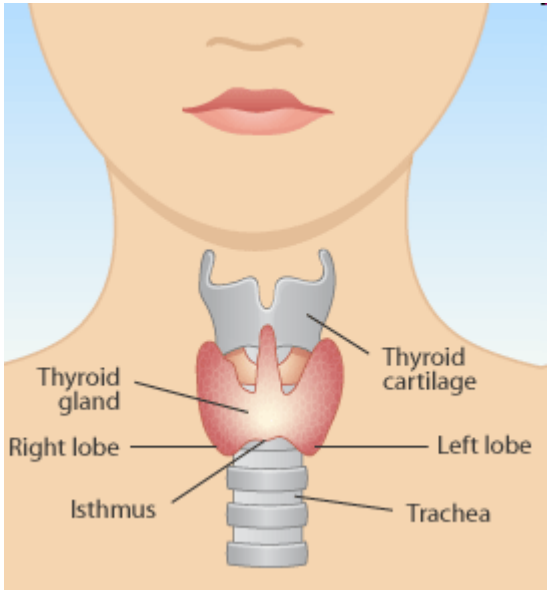
I. Fetal and neonatal thyroid gland

II. Congenital hypothyroidism

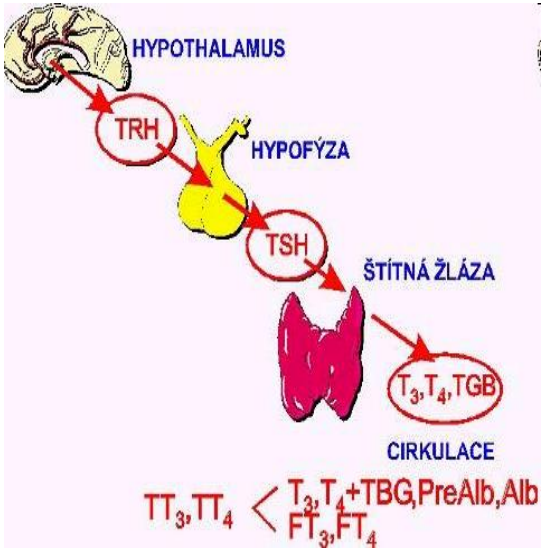
III. Thyreopathy in childhood and puberty



Picture from www.stitnazlaza.estranky.cz

Thyroid hormones (TH)

- TH stimulate metabolism and energy uptake in almost all cells in the body
- In children TH stimulate growth, development and differentiation of the cells
- Crucial for the growth and development of central nervous system in the „critical period“ until 3 years of age



Acc. to Doc. SChneiderka, VFN

Pregnancy

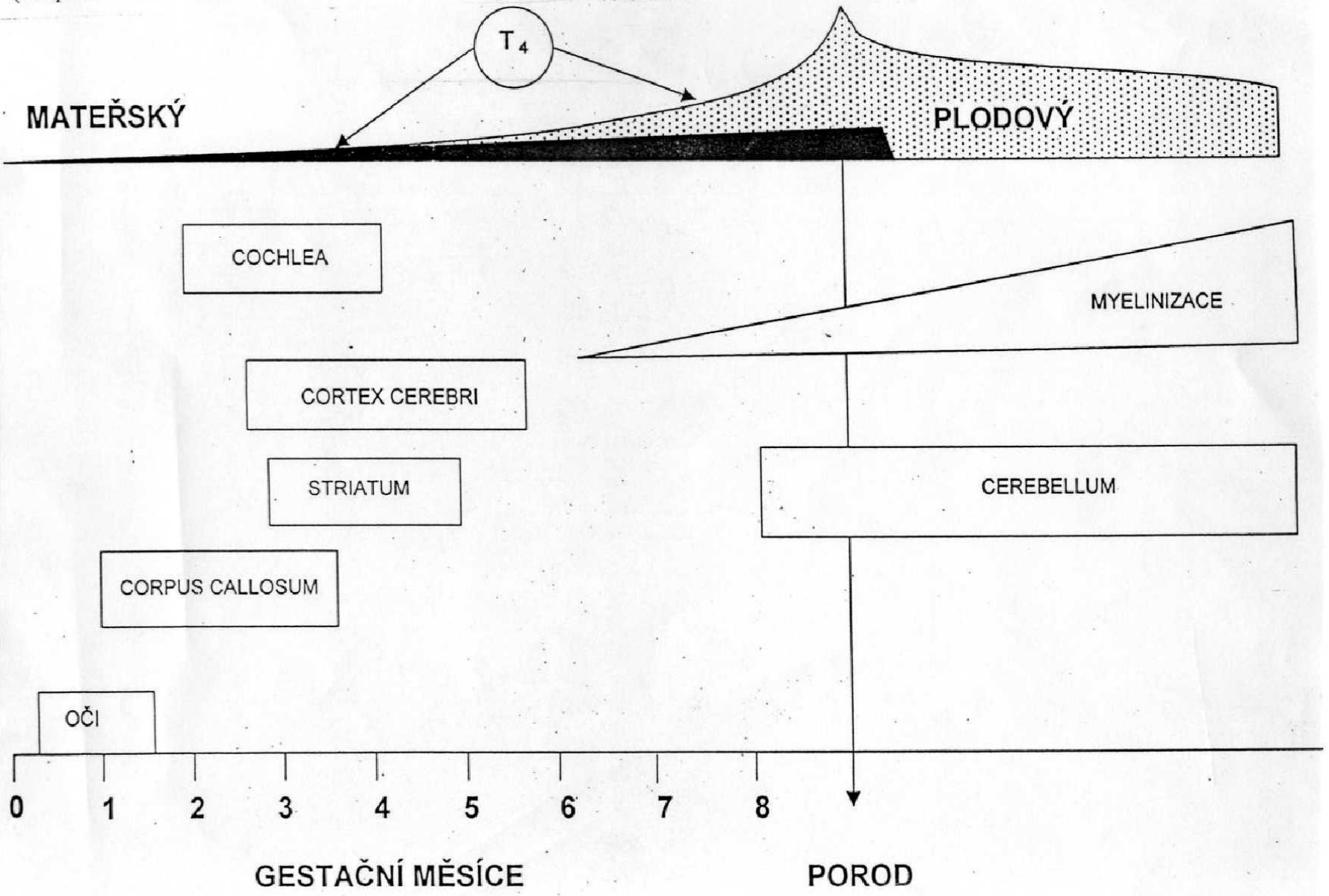
- Embryonal period: maternal thyroxin penetrate through coelom cavity (*transthyretin*)

- After 3rd month of pregnancy – only 15-20% of maternal thyroxin come through placenta
- Low levels of thyroxin in the mother in first six moths of pregnancy – bigger impact to the intellectual and motoric development of the fetus

  - Impairment of brain development, growth and migration of the neurons, synaptogenesis and myelinisation

  - Congenital hypothyroidism – in the fetal period has the child thyroxin from the mother

Schema časového rozložení vývoje hlavních útvarů v mozku ve vztahu ke změnám zdrojů a nabídky T4 během nitroděložního období
(adaptace dle: DeLong,R.G., 1993)



Recommendation for jodid uptake WHO, UNICEF 2001

Age	Recommended iodine uptake ug /day	Joduria (iodine in urine ug l/L
Pregnant, Brest-feeding	200	150
neonates	90	180-220
Children 6-36 month	90	100-200
Children 6-12 years	120	100-200
adolescents	150	100-200
adults	150	100-200

Congenital hypothyroidism (CH)

- Definition: : deficiency of TH or their utilization in the peripheral tissues in prenatal period

Types:

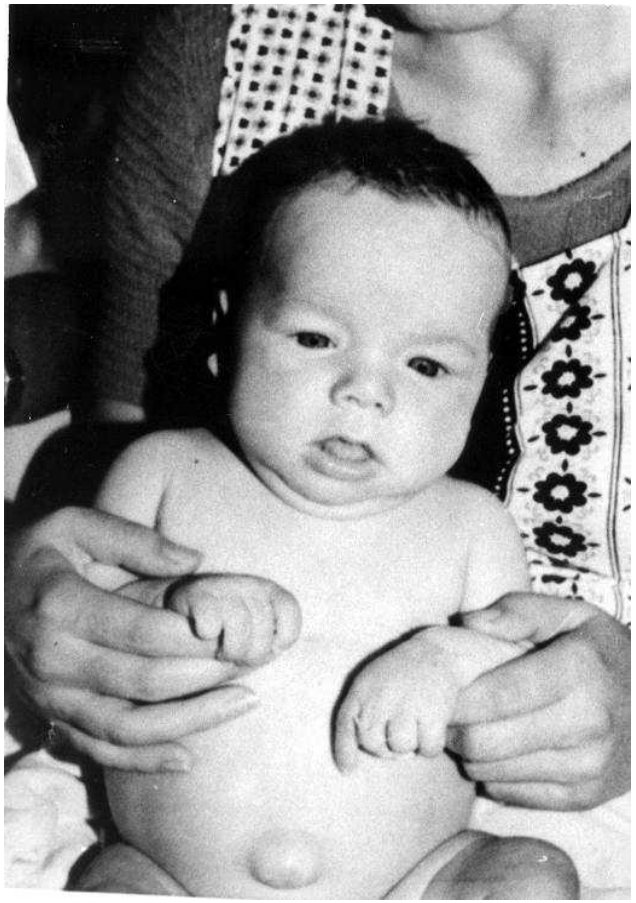
- 1. Transient KH endemic *primary*
  - Various level of damage of brain development in neonatal – is irreversible
  - Impact of deficiency of iodine uptake in mother and fetus during the pregnancy (regions with iodine deficiency in the population → cretinism, endemic cognitive dysfunction).
- 2. Transient KH sporadic *primary*
  - ↑↑↑ Autoimmune antibodies in mother - rarely

Picture from Cs.sweswe.net

Congenital hypothyroidism (CH)

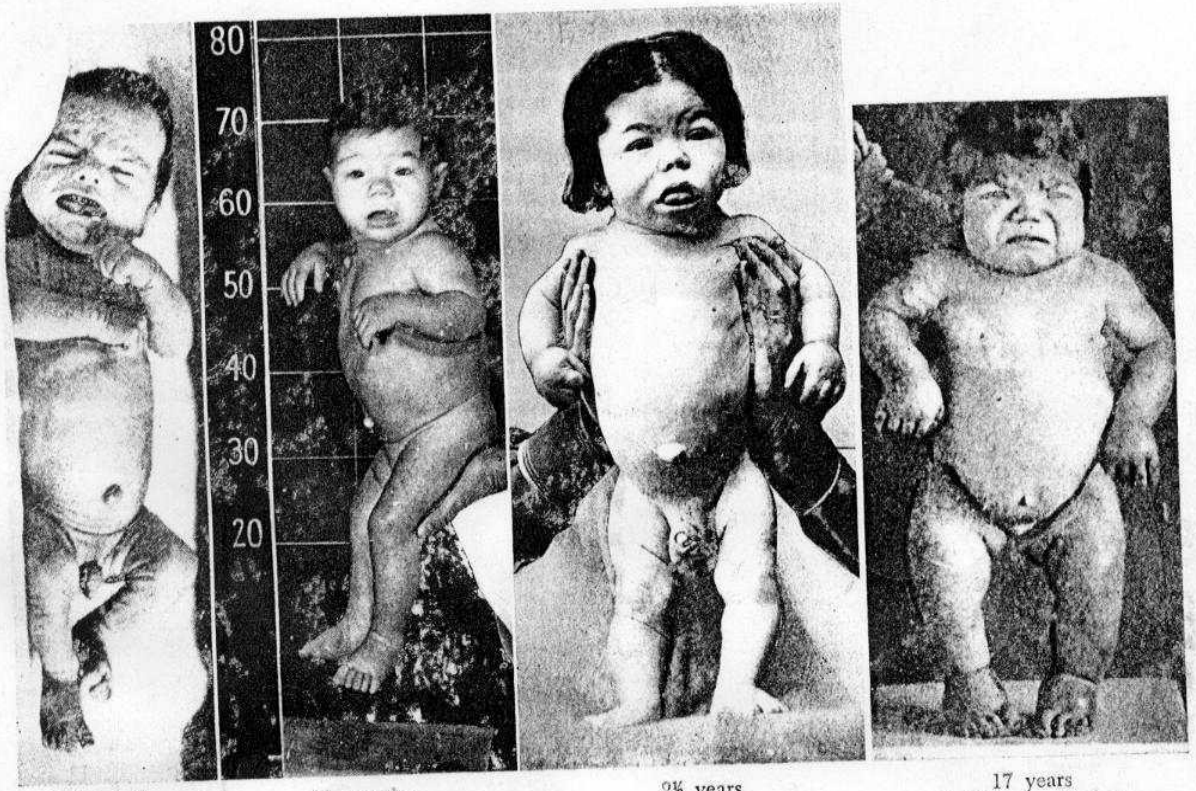
- Neonatal period:
  - Icterus prolongatus neonatorum
  - Persistent back fontanel

- Toddles period
  - Macroglosy
  - Subcutal edema
  - Deterioration of food uptake
  - Hernia
  - Constipation
  - Muscle hypotonia
  - Growth retardation
  - Lethargy
  - Horse cry
  - Retardation of bone and tooth maturation



TYPICAL UNTREATED CRETINS

Characteristics Becoming More Obvious with Advancing Age



5 months | 11 months | 2½ years | 17 years
Height age: 18 mos.

Four patients of different ages who show characteristic signs of cretinism. All had grayish circulatory mottling and decreased temperature of skin. *Note the puffiness of features, thick tongue, and loose redundant skin. These myxedematous signs cause the grotesque, ugly appearance which is not encountered in all cretins.*

NOTE that the features remain infantile and growth is retarded so that the patients seem more and more abnormal as they grow older.

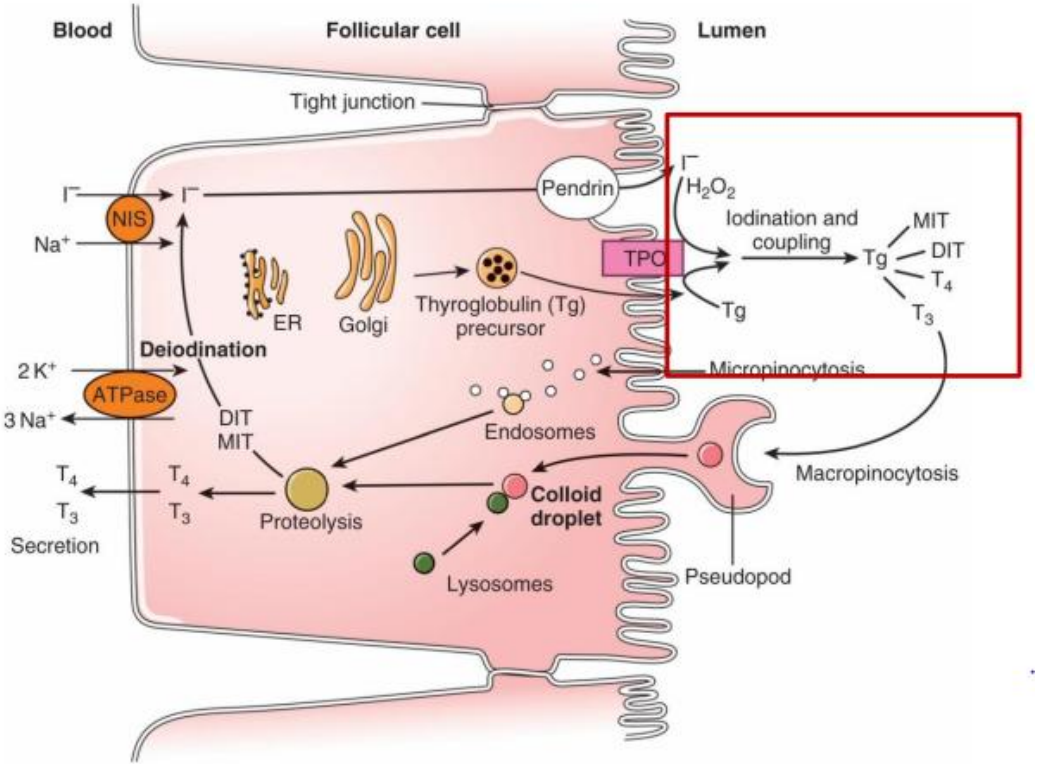
CHAPTER VI—FIGURE 11

ATLAS of CLINIC. ENDOCRIN. [LISSER A.B., ROBERTO F., - 1962 - St Louis]

Permanent sporadic CH

- Peripheral, primary:
  - Dysgenesis (65%): morphological failure of thyroid glad development
  - Dyshormonogenesis (30%): failure of synthesis of TH
  - Resistance of peripheral tissues to TH (rarely): connected with ↑TSH, ↑T4,T3

DYSHORMONOGENESIS		
TPO (inheritance AR, AD),THOX2	**goiter**	
Pendrin (Pendred syndroma)	**goiter** eufunction, hypofunction	CNS – cochlea, deafness, malfunction of membranous labyrinth
DEHAL (dehalogenasis)	**goiter**	
Tyreoglobulin	**goiter**, hypofuntion	
NIS (natrium-jodide symporter)	**goiter** postnatally	



www.medicinnoter.dk

DYSGENESIS		
TSH receptor	Variabile (hypo, athyreosis)	
TTF-1 (transkription tyreoidal factor), NKX2.1,Diferentiation of TG	hypoplasia	Lungs – deficiency of surphactant Brain – pit. cysts, ataxia
TTF-2 Bamfort syndroma Descending of TG	Ektopia, hypoplasia	Disturbances of middle line development (cleft palata, choan atresia, spiky hair)
NKX2.5	Ektopia, hypoplasia, Hemithyroidea, cystic malformation	
PAX8 differentiation of folicullar cells	Ektopia, hypoplasia, hemithyroidea	Malformation of kidney cryptorchism

Secondary / tertial CH

  - Very rarely
- Hypopituitary – mutation in the gene for:
  - rTRH-beta subj. → deficiency of TSH
  - Transcription factors → mild hypothyroidism, multihormonal insufficiency
  - TF Prop -1 (GH,TSH,PRL,FSH,LH)
  - TF LHX -3
- Hypotalamic:
  - TRH-beta subj. – serious hypothyroidism

Screening of CH – TSH levels

- Dry blood drop 48-72 hours after birth
- Secondary screening: 10-14 day after birth
  - In children with low birth weigh under 1500g
  - In children with serious disease (on intensive care unit)
  - After exposition of iodide (iodine antiseptics)
  - After treatment with dopamine
  - Always before exchange transfusion

- Incidence 1:4320
- gender 2:1 (more girls)
- Treatment with thyroxin within 14 days

Substitution of hypothyroidism

Age	L-T4 ug/kg/day
Neonates	10-15
Toddlers	8-10
Preschool children (1-6 years)	5-8
School children (6-12 years)	2-4
Adolescents (over 12 years)	2-3

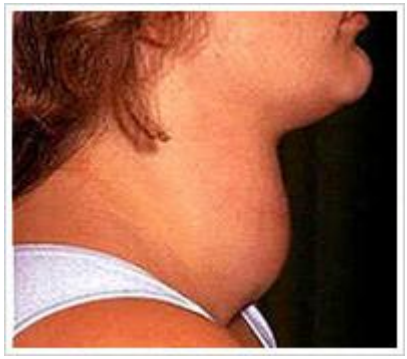
Neonatal thyreotoxicosis

- Permanent – rarely
  - Mutation in the gene for rTSH, activation of the alfa subunit of the G protein
- Transient - transplacentaly transmission of Ab against TSH receptor
  - 3-12 weeks – 5 months a.b.
  - Mortality up to 25%!
- Impacts: fetus – craniosynostosis, mikrocephaly, growth retardation, goiter, tachycardia
- Neonates – failure to thrive, unease, heard insufficiency, tachycardia

- Treatment: thyreostatics, digitalisation, iodide (Lugol solution), corticoid therapy

Thyreopathy in childhood and puberty

- Goiter
  - Iodopenic
  - Autoimunne
    - Juvenile lymphocytary thyroiditis
    - Juvenile thyreotoxikosis GB



- Thyreoidal tumors

Investigation of thyroid gland

Stage O. - normal

I. - backward bend of head : A - palpation, B- visible

II. - normal head position - visible

III. - visible from doors

Picture from www.lidovky.cz

Autoimunne thyroiditis (AITD)

Hypertrophic variants:

- Juvenile thyreoiditis -Hashimoto (AIT)
  - goiter in 99 %
- Juvenile Graves Basedow disease (JGD)
  - goiter in 75 %

Atrophic variant:

- Atrophic thyreoiditis – very rare in children

AITD

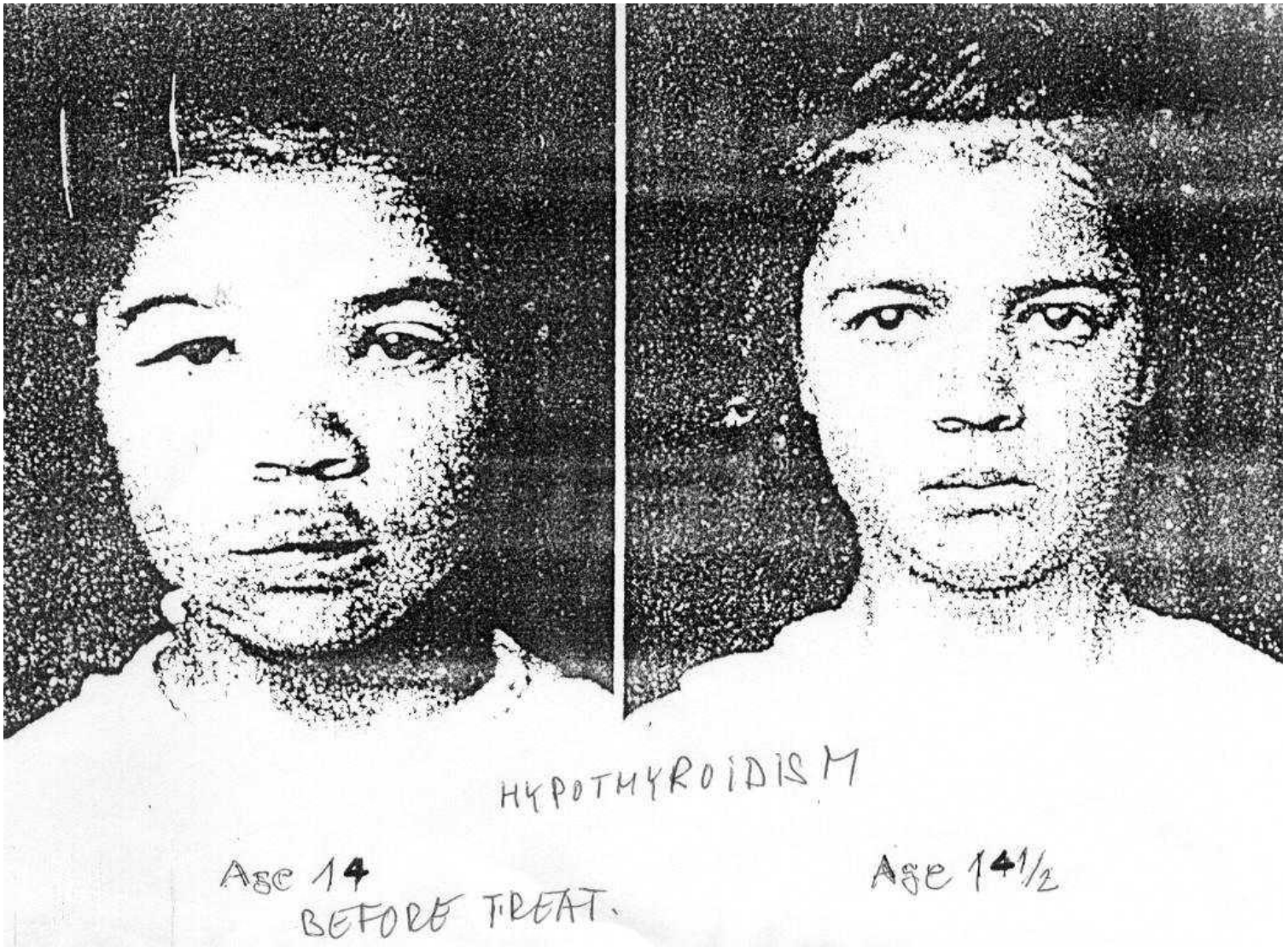
- Can be connected with others autoimmune disease
- Combination with T1DM
- APS I. (Adison disease, hypoparathyreosis, mucocutan candidosis)
- APSII.
  - Schmidt sy. (AIT, Adison dis.)
  - Carpenter sy. (AIT, T1DM, Adison dis.)

AITD

- Ethiology – genetic (HLA II.class, CTLA-4)
- Nongenetic
  - Endogenous factors – more frequently in woman
  - Low bw – higher risk of AIT in adults
  - Infections – viral
  - Environment
    - High iodine uptake (impact to development and function of immune cells)
    - Smoking
    - radiation

AITD – acquire hypothyroidism

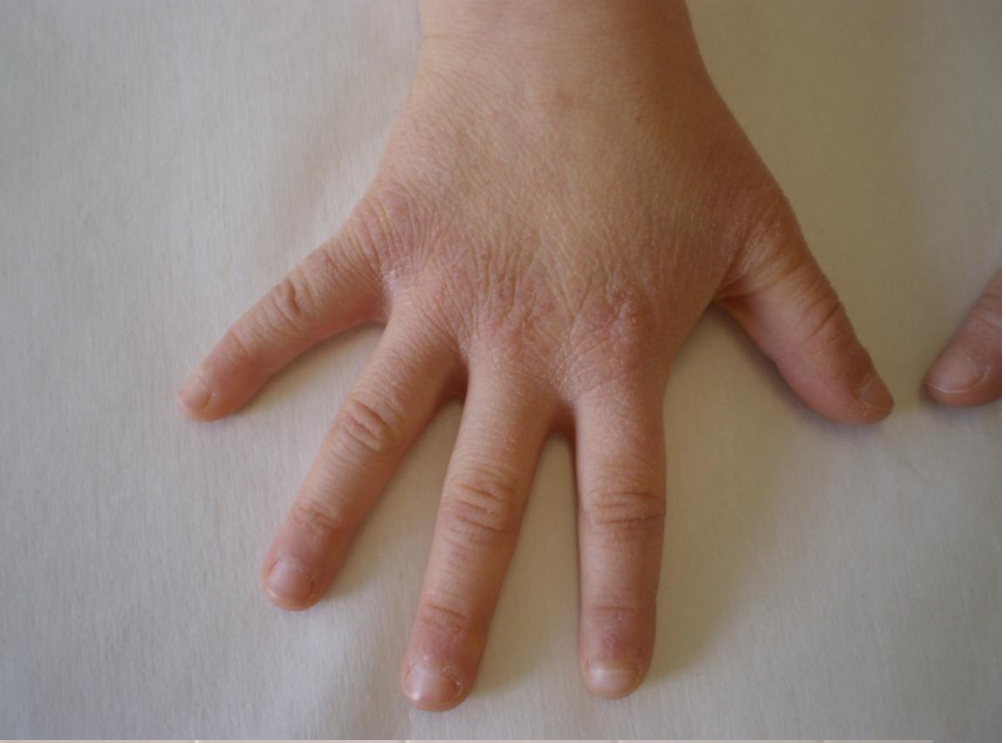
- Facies hypothyreoidea
- Periorbital edema
- lethargy
- Failure in school
- Growth retardation
- Gaining weight (obesity)
- lipid metabolism changes
- Muscle weakness
- Coldness intolerance
- Paleness of skin and mucosa (macrocytal anemia)
- Dry skin (chronic ekzema)
- Pericardial effusion
- Goiter



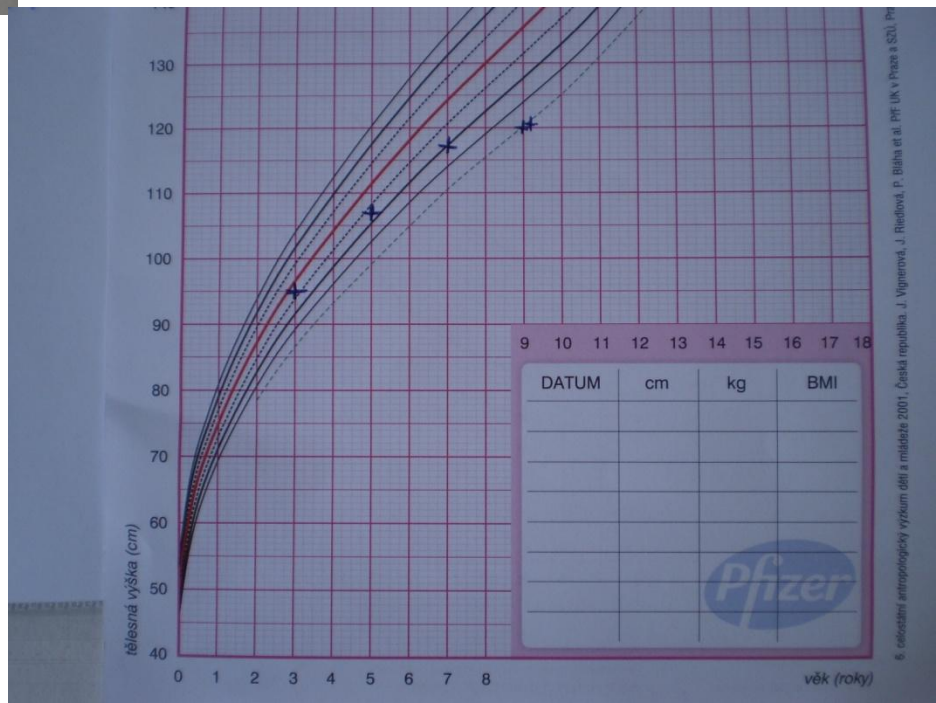
HYPOTHYROIDISM

Age 14
BEFORE TREAT.

Age 14 1/2

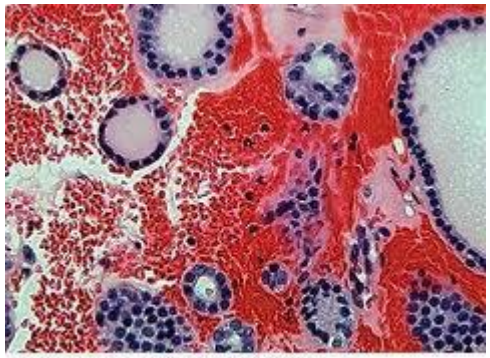


Picture from Prof. Lebl

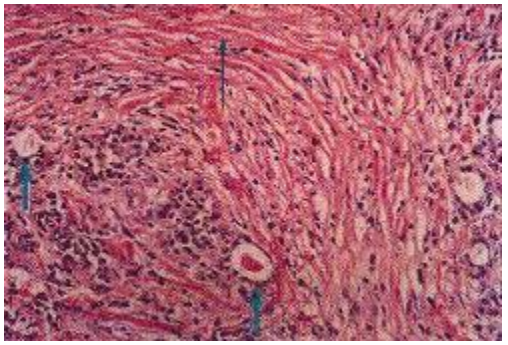


Juvenile lymphocytal thyroiditis (AITD), Hashimoto

- Prevalence 2 - 5 % in peripubertal age
- 9-10 x more in girls
- Manifestation :
  - goiter
  - thyroid function :
    - Eu-function 60%
    - transient hyper-function 10% (destruction of folicular cells goes to washing up the TH)
    - Hypo-function (hypothyroidism) 30%, more frequent subclinical – normal fT4, high TSH)



Histologie normální štítné žlázy.
Foto: pixcam.com



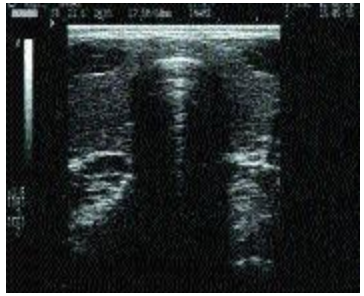
AITD – diagnose and treatment

- Diagnose:
  - fT4, TSH
  - Autoantibodies (anti TPO, anti hTG, TRAK)
  - Palpation of thyroid gland
  - UZ of TG, event. FNAB
  - ECHO

www.ulekare.cz

- Treatment:
  - Always by hypothyroidism (TSH over 4,5): L-thyroxin
  - Always by hyperthyroidism: Carbimazol (mostly transient)
  - Others variants of L-thyroxin treatment – not evidence based: to reduce the goiter, to reduce the autoimmune process, prevention of the cancer in the adult

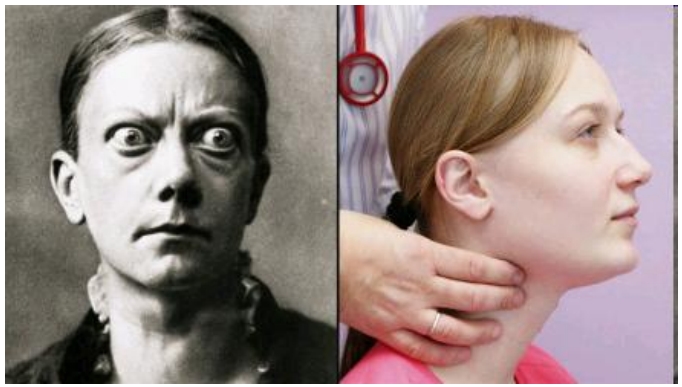
- Prognosis: getting fibrose, getting hypo-function
  - In 5% spontaneous curing



Juvenile Graves-Basedow dis. JGB

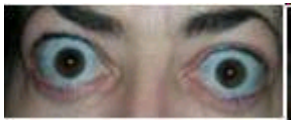
- 99 % hyperthyreosis in childhood, 2-5% of all thyreopathies
- 8x more in girls
- Infiltration of thyroid gland with lymphocytes (T, B cells) → production of stimulating Ab against TSH receptor (TRAK, rTSH-Ab)
- → stimulation of receptors on the folicular cells and high secretion of TH→ hypermetabolism
- Remission of the disease is followed by relaps

- Manifestation:
  - Hypermetabolism (100%, losing weight, diarrhea, unease, sweating)
  - Tachycardia (100%, with hypertension)
  - Goiter (75%, size of the thyroid gland is a marker of the success with treatment)
  - orbitopathy (60%, only rarely malign)



Picture from www.doma.nova.cz

JGB



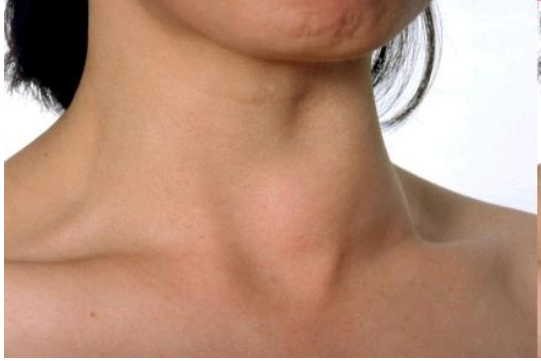
- Laboratory diagnosis:
  - fT4, TSH, anti TPO, anti hTG, TRAK, SHBG, T3
  - TRAK ↑↑ in 90 %, antiTPO ↑ in 80 %, antihTg↑ in 75 %
  - UZ of thyroid gland

- Pharmacological treatment
  - Inhibition of TH synthesis:
    - Carbimazol 0,5 mg/kg/day (3 times a day)
    - Tyrozol 0,3-0,5 mg/kg/day (1-2x/day)
  - Peripheral deiodation: Propycil 5 mg/kg/day
  - Beta-blockers

- Surgery treatment: total thyreoidektomy followed by substitution of thyroxin

- radio iodide: destruction of the gland, in childhood very rarely

Nodular goiter



- Benign: **(cca70%)**
  - Multinodullar goiter (AITD)
  - Solitary node - in 70% *cysts, benign adenoma*

- MALIGNANT nodes (up to 30%)!!!

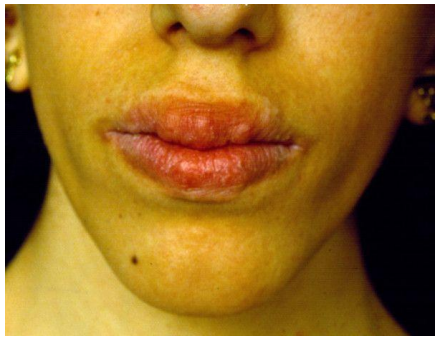
  bois: girls = 1:2, euthyroid (rarely hyperthyroidism with microcarcinoma)
  - histology: mostly papillary or folicullary carcinoma,
  - treatment : total TE, radioablation of the thyroid gland residues, substitution of the hormones and suppression of the TSH
  - Follow up whole life – thyreoglobulin levels
  - prognosis good

  - Non-folicullary carcinoma - from parafolicullar cells -
  - medullary carcinoma
  - Metastasis from another tumors

(Picture from www.doplnek.com)

Medullary carcinoma

- From parafolicullar C cells
- sporadic (75%) and familiar (25%) - AD inheritance
- specific Tu marker : Thyreocalcitonin (sensitivity ↑with Ca a pentagastrin
- FMTC only – familiar medullary ca
- MEN (multiple endocrine neoplasia)2A
  - Medullary ca, adenoma of parathyreiod cells, pheochromocytoma
- MEN 2B
  - medullary Ca
  - mucocutal neurofibroma
  - marfanoid habitus)



Characteristic phenotype of MEN 2B including thickened lips with bumps.
Italian Journal of Pediatrics2012**38**:9

- PREVENTION !!! –
  - Genetic investigation – mutation in RET proto- onkogene
  - Until 5 years of age → prophylactic thyreoidektomy in children with mutation (from the known families)
  - Goal: prevent developing of the tumor
  - Follow up: substitution of the L-T4, thyreocalcitonin levels