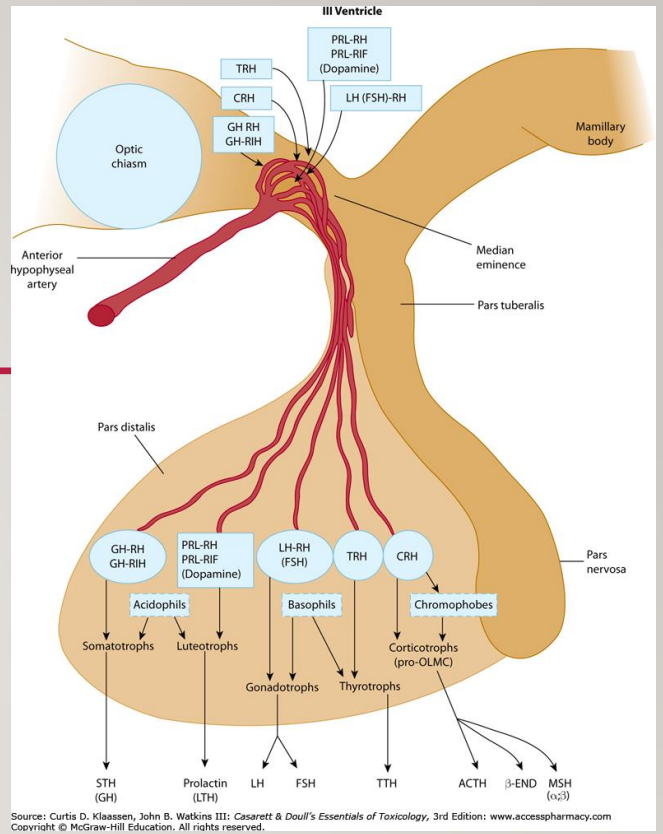
PEDIATRIC ENDOCRINOLOGY II.

J. KYTNAROVÁ , KPDPM 1. LF UK A VFN

ADENOHYPOPHYSIS

- TSH
- gonadotropins - LH, FSH
- PRL (prolaktin)
- GH (growth hormone)
- ACTH (adrenocorticotropic hormone)



ADENOHYPOPHYSIS SIGNS AND SYMPTOMS

- **1. Altered endocrine function**
- a. **Hypofunction** - all hormones (panhypopituitarisms)
- - 1 or 2 hormones (congenital is more common)
- b. **Hyperfunction** - usually 1 (2) hormones

2. Local symptoms

Headache - tumor pressure

- Bitemporal hemianopia (GH, PRL) - pressure on chiasm

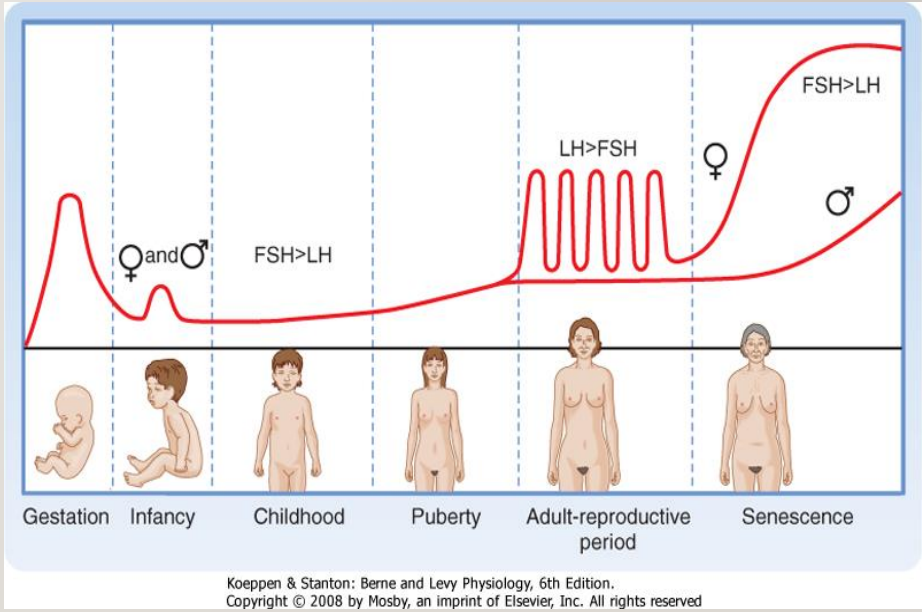
GONADOTROPINS - LH, FSH FUNCTION

	women	men
LH	↑ Estrogen synthesis Ovulation → corpus luteum development	↑ Testosterone synthesis in Leydig´s cells
FSH	Ovarian follicle development	↑ Spermatogenesis ↑ Testicular growth

GONADOTROPINS – SECRETION DYNAMICS

- **„Minipuberty“**
- Hypothalamus - hypotalamus – pituitary – gonadal axis activation after delivery
- High levels of gonadotropins first 4 -6 months of age
- Prepubertal low levels until the expected onset of puberty

- **Influence**
- **Testicular descent**, growth of testicular volume and penis
- Absence of minipuberty in boys- micropenis, testicular retention
- Girls - telarche, ↑ levels last for 2-3 years → telarche
- Postmenopausal levels in girls with gonadal dysgenesis (Turner syndrome)



HYPOGONADOTROPIC HYPOGONADISMS

- **Congenital**
- Hypothalamic or pituitary dysfunction
  Isolated or combined deficit
  Congenital malformations of central CNS structures
  Some genetic syndromes
  Mutations of more than 50 genes (KAL1, HESX1, KISS1, DAX 1 ..)
  Combined hormone deficiency – e.g. PROP1 gene
  Acquired - tumor, trauma, autoimmune hypophysitis, degenerative diseases, radiation
  Functional - chronic diseases, anorexia nervosa

HYPOGONADOTROPIC HYPOGONADISMS GENETIC SYNDROMES

Kallman syndrome - XR

- Prevalence 1/7 500
- hypogonadisms
- Lack of sense of smell (hypoosmia/anosmia)
- **Laurence-Moon-Biedl syndrome - AR**
- Cerebellar ataxy, spastic paraplegy, PMR, polydaktyly, obesity, retinitis pigmentosa, hypopituitarisms, short stature..)

Source: Labhart A. Clinical Endocrinology, 1974

PRADER - WILLI SYNDROME (PWS)

- **Prevalence 1 /10 000-16 000**
- **Genetics**
- **Paternal deletion on chromosome 15,** 11q-13q (70%)
- (maternal deletion – Angelman syndrome)
- **uniparental disomy** (25-30%)
- (inherited two copies of chromosome 15 from the mother and no chromosome 15 from the father)
- **Imprinting defect** (1-3%)

PWS – SIGNS AND SYMPTOMS

- **Infants**
- **Poor muscle tone** (hypotonia) - improving
- **Poor sucking reflex -** Failure to thrive
- **Craniofacial dysmorphia** (distinct features)
- almond-shaped eyes
- a narrowing of the head at the temples
- a turned-down mouth and a thin upper lip („carp“)
- **Underdeveloped genitals (hypogonadism)**
- small penis and scrotum. Cryptorchidism. In females, the clitoris and labia may be small.

PWS – SIGNS AND SYMPTOMS

- **Childhood to adulthood**
- **Hyperphagia** – food craving, 2nd – 3rd year of life
- **Obesity** – central, severe
- **Mental retardation**
- Short stature, acromicria
- Hypogonadisms, hypogenitalisms
- Metabolic syndrome
- Sleep apnea syndrome

PWS - PATHOPHYSIOLOGY

- **hypothalamic-pituitary region impairment**

- **Regulation of food intake -** hypothalamus
- **Growth hormone deficiency**
- **Hypogonadotropic hypogonadism**
- hypogenitalism (small external genitalia), testicular retention,
- delayed or incomplete puberty
- **ACTH deficiency? -** (partial, about 60% of patients)

PWS - THERAPY

- Weight control (reduction)
- ↓energy intake
- ↑ physical activity
- bariatric – metabolic surgery
- Growth hormone therapy
- Sex hormones substitution
- Psychological problems, school
- Correction of scoliosis, eye defects,
- testicular retention…

PWS – GROWTH HORMONE

- ↑ growth velocity, ↑ growth of acral parts of the body
- ↑ muscle mass
- ↑ muscle strength
- BMI does not change only with GH treatment!
- Reduction of adipose tissue, reduction of skin folds thickness
- ↑ activity and responsiveness
- **Laboratory findings** - ↓ cholesterol, ↑ HDL, insulin levels unchanged
- **Adverse effects** - Diabetogenic effect not confirmed
- Scoliosis (obesity + hypotonia + rapid growth in the treatment of GH)

HYPERGONADOTROPIC HYPOGONADISMS

Congenital (dysgenesis, steroidogenesis blocks …)
Acquired (gonadektomy, inflammations, radio or chemotherapy) …)

	Boys	**Girls**
Genetic causes	**Klinefelter syndrome** (47, XXY or variants)	**Turner syndrome** (45, XO, mosaics with line 45,X, structurally altered X)
	XX male	
	Noonan syndrome	**Noonan syndrome**
Other causes of primary gonadal failure (testicular/ovarian)	**Gonadal dysgenesis**	**Gonadal dysgenesis**
	Anorchia/cryptorchidism	Oophorectomy
	Irradiation	Irradiation
		Oophoritis
		Galaktosemia

TURNER SYNDROME

- **1/ 2000 -2500 born girls**
- **Genetics**
- Monosomy 45,XO
- Mosaics 45,XO/46, XX or 45, XO/46, XY
- Structurally altered X chromosome

Karyotype 45X0/46XX

TS – SIGNS AND SYMPTOMS

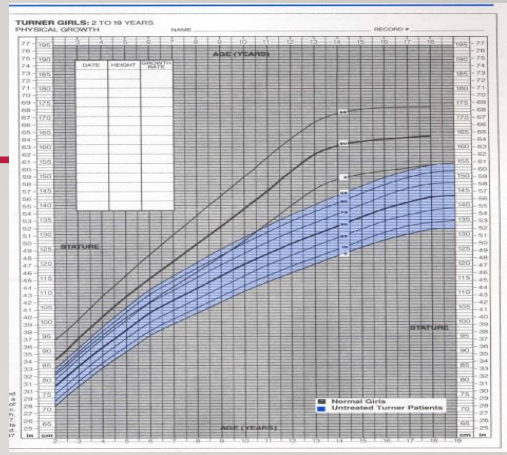
Signs and symptoms	Frequency (%)
Short stature (SHOX gene missing)	95 -100%
Gonadal dysgenesis	95 - 98%
a wide, webbed neck	80%
lymphedema of the hands and feet - congenital	51%
Pigmented nevi	45%
Congenital renal defects	40-60%
Congenitah heart defects	25%
AITD	25-60%
Celiak disease	10%

Others signs: broad chest and widely spaced nipples , cubiti valgi, recurrent otitis, myopia…..)

TS – SIGNS AND SYMPTOMS

Newborns	**Typical dysmorphia** **Lymphedema** **webbed neck** **Congenital heart, renal defects**
Childhood	**Growth impairement**
Adolescence	**Gonadal dysgenesis** **(delayed puberty)**

TS – THERAPY – SHORT STATURE



20th century ……...

Low doses of estrogens, anabolic steroids

Improved growth velocity

Precocious closure of growth plates

Elongation of lower limbs according toIlizarev

Growth hormone

1960 - The first use, GH extracted, uses sporadic

Mid-1980s - recombinant growth hormone

Pharmacological doses (about 2x higher than substitution)

1991 - Indication registered in the Czech Republic for the treatment of GH deficiency

TS – OVARIAN FAILURE THERAPY

- ***Aim of the therapy***
- Secondary sexual characteristics development
- Induction of menstrual cycle
- Ensuring the growth of internal genitals
- Preservation of bone density
- Prevention of CVD and metabolic diseases

TS – ASSISTED REPRODUCTION

- Sterility in women with TS in 95 - 98%

- Oocyte donation → opportunity to experience pregnancy and have a complete family!

TS – LONG-TERM TREATMENT RESULTS

- **Socially acceptable height (even over 160 cm!)**
- early initiation of GH treatment
- treatment at optimal dose and schedule
- coordination of treatment with initiation of sex hormone replacement
- (first miniestrogenization)
- **Puberty and menstrual cycle**
- **Possibility of establishing a family**

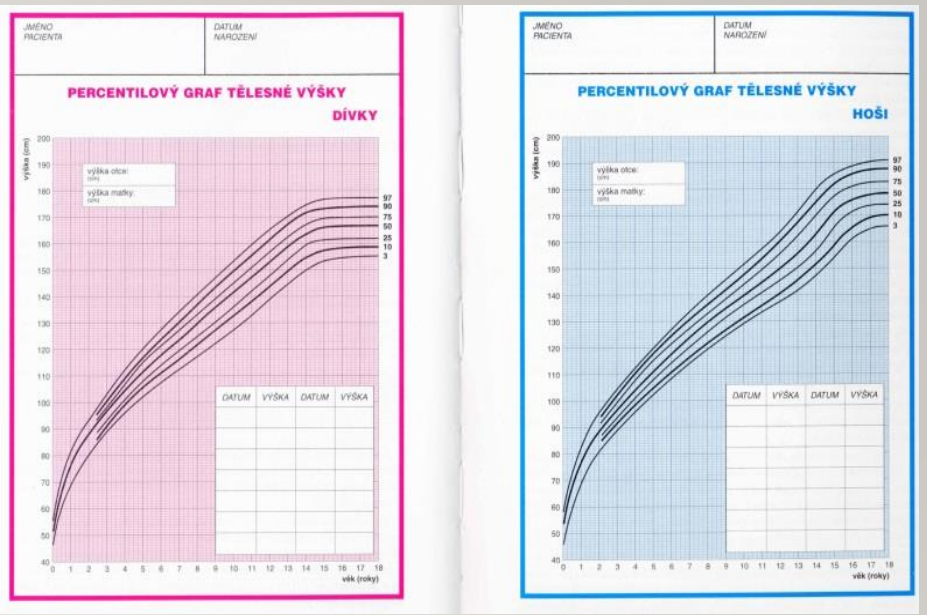
GROWTH HORMONE AND GROWTH

- **Effects**
- **Growth** - indirect effect on the chondrocytes through IGF-I
- **Anabolic effect -** ↑ proteosynthesis, ↑ muscle mass
- ↑ lipolysis
- **Counterregulatory hormone insulin,** ↑ gluconeogenesis
- **Serum levels -** vary considerably during the day! released in waves,
- adults - <2 mIU / l, young men> 100 mIU / l

LINEAR GROWTH

- **<u>Environmental factors</u>**
- Nutrition (malnutrition)
- season (↑ growth velocity in spring and summer)
- Physical activity
- **<u>Genetic factors</u>**
- Parents´ height
- gender - men are on average 13 cm taller than women
- race

GROWTH



- Height (percentile charts - VI. CAV - national study)
- Growth curve from birth
- Growth velocity (cm / year)
- **Expected range of growth according to genet. disposition**
- **Midparental height** (+3 cm - secular trend)
- Mother's height + father's height / 2
- boys: F (O) - height, M- height + 13
- girls: F (O) - height - 13, M - height
- Bone age – X ray of left wrist, BA/CA

SHORT STATURE

- **Familial small stature**
- BA is not delayed
- The growth range corresponds to the expected one
- Cave! Unknown AD disease in a parent?
- **Constitutional delay in growth and puberty**
- delayed bone maturation
- delayed onset of puberty in otherwise healthy children
- familial occurrence

SHORT STATURE – ENDOCRINE DISEASES

- **<u>Endocrine disorders – decreased growth velocity!</u>**
- 1.**Growth hormone deficiency – first sign**
- **2. Hypothyroidism - may be the first sign**
- **3. Hypercortisolemia – together with obesity first sign**

- 4. Diabetes mellitus - poorly compensated, it is not diagnostic sign
- 5. Precocious puberty, pseudopubertas praecox (CAH) - late consequence

GROWTH DISORDERS

- **Psychosocial growth retardation**
- **Nutritional - ** kwasiorkor, marasmus, mental retardation
- **Gastrointestinal**
- **a. malabsorption –** celiac d., Idiopathic bowel disease, cystic fibrosis
- **b. liver diseases –** chronic hepatitis, glycogen storage d...
- **Heart diseases** (severe congenital heart defects)
- **Respiratory d. (**cystic fibrosis)
- **Renal d. (**chronic pyelonefritis, Fanconi sy, chronic renal insufficiency)
- **Bone metabolism -** rickets, vitamin D resistant rickets, osteogenesis imperfecta, achondroplasia, Turner syndrome)
- **Genetic disorders –** chromosomal aberations

FGR (IUGR/SGA)

85% postnatal catch up growth
15% postnatal growth failure
Many theories
Central fat distribution
Early puberty
Early metabolic syndrome

Noonan syndrome

1: 1000 – 25000 live born children
Inheritance: AD, de novo, several genes (8)
-RASopathies

Short stature
Mild PMR
Turner – like syndrome
Webbed neck
Congenital heart defects
Boys – testicular retention

Silver – Russell Syndrome

1: 20 000

IUGR
Growth failure
Failure to thrive
Typical face
Hypoglycemia

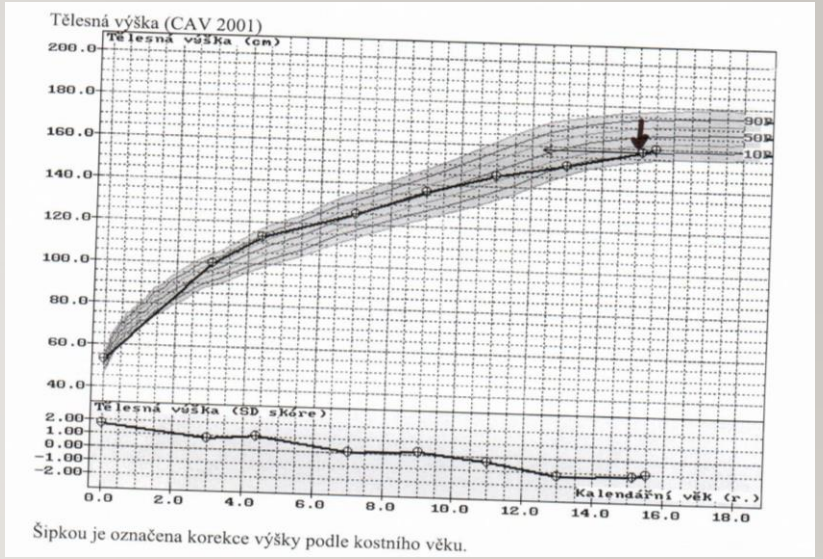
Case report – 15 years old girl - her diagnosis?

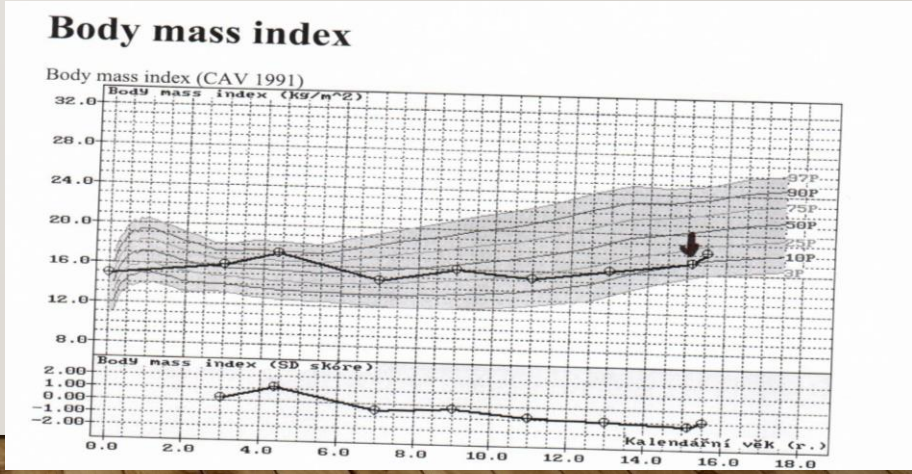
Present illness: girl, 15 years
2 years treated for **mikrocytic anemia**
Decreased growth velocity from 9 years
Onset of puberty at the age of 14,5

Physical examination: height 158,5 cm (13. centile),
growth velocity 3,5 cm/year!, weight 43.2 kg, BMI 17,2 (10 .centile)
BP 132/67, HF 104/min
Pale skin, Tanner M2, P1,

BA : 12,29 years, i.e. below 1. centile

Laboratory results:
CRP.: **52,2** mg/l, **FW 22/58**
Blood count- Leu: 7,02 10^9/l, Ery: 4,70 10^12/l, HB: **83** g/l, HTC: **0,300** 1, MCV: **63,8** fl, Plt: **431** 10^9/l,





Fecal kalprotektin 453 ug/g(↑)

MRI enterography:
The finding corresponds to multi-stage involvement of the small and large intestine in Crohn disease

Histology
Conclusion: Rectal microgranulomas were found in the rectum sample. The nature of the above-described changes does not exclude clinically suspected Crohn's disease if the clinical course suggests it.

Conclusion: Crohn disease

GROWTH DISORDERS – EXAMINATION

- **1. Anthropometry**
- **Height** below 3. centile with respect to CA and / or
- **Decreased growth velocity** (below 25. centile/ below 4 cm/year)
- **2. History**
- Prenatal and perinatal insult
- Birth weight, length, growth curve
- Food intake, stools
- Family history of short stature, delayed puberty

GROWTH DISORDERS – EXAMINATION

- FW, blood count
- Biochemistry
- Urine- chemical, microscopical, eventually culture
- fT4, TSH
- IGF1
- Antibodies against transglutaminase
- Girls – karyotype
- Bone age
- Suspected GH deficiency - dynamic tests - klonidin, arginin, insulin…
- MRI CNS

GH DEFICIENCY - CAUSES

- **Congenital deficiency**
- Disorders of pituitary morphogenesis (usually associated developmental anomalies)
- Pituitary differentiation disorders (eg PROP1, POU1F1)
- Isolated STH deficiency - genes directly controlling STH synthesis
- **Acguired deficiency**
- Middle line tumors (craniopharyngeoma, germinoma, optic glioma)
- Langergans cell histiocytosis
- Radiotherapy
- Trauma, hydrocephalus… ..

GH DEFICIENCY – SIGNS AND SYMPTOMS

- **newborns** - hypoglycemias
- - births length and weight normal
-
- **Children** - growth retardation
- - decreased growth velocity
- - relative central obesity
- - immature ("doll") face, prominent frontal bones, wide nose)
- - delaeyed BA and onset of puberty

GH DEFICIENCY - THERAPY

- **Therapy –** recombinant GH daily s.c. in the evening
- **Indications for GH therapy**
- GH deficiency
- Turner syndrome
- Chronic renal insufficiency with growth failure
- Prader – Willi syndrome
- FGR (SGA/IUGR) with postnatal growth failure
- Noonan syndrome (RASopathies)

ADRENAL GLANDS

- Adrenal cortex –mesoderm
- Zona glomerulosa –mineralocorticoids production
- Zona fasciculata, reticularis – glucocorticoids, androgens
- Adrenal medulla - ektoderm
- katecholamins

ACTH

- **Effects**
- Adrenal cortex stimulates
- production of glucocorticoids,
- mineralocorticoids and androgens

ACTH – REGULATION

- **Regulation of ACTH secretion**
- 1. Congenital diurnal rhythm
- 2. Closed negative feedback
- 3. Open feedback - stress

- **ACTH levels - 10-60 ng / l**
- peak at 5-8 o'clock in the morning, lowest levels - at midnight

PRIMARY ADRENAL INSUFFICIENCY

Congenital genetic disorders	**Congenital adrenal hyperplasia** **Adrenoleukodystrophy** Adrenal hypoplasia Tripple A syndrome, familial glucocorticoid deficiency Smith – Lemli-Opitz syndrome and the others….
Autoimmune diseases	**Isolated autoimmune adrenalitis** Autoimmune polyglandular syndrome
Infections	**Meningococcal sepsis** (Waterhouse-Friderichsen syndrome) Tuberkulosis, AIDS…
Other acquired causes	**Bilateral bleeding** (meningococcal sepsis, traumatic delivery, anticoagulant treatment…)
Infiltration	Amyloidosis, hemochromatosis, sarcoidosis.. (rare)
Iatrogenic causes	Adrenalectomy – bilateral, drugs….

SECONDARY ADRENAL INSUFFICIENCY

Congenital or genetic causes	Developmental abnormalities of the CNS Combined pituitary hormone deficiency (eg PROP1) ACTH deficiency isolated
Acquired causes	**Tumors** of the pituitary and hypothalamus (adenoma, cranyopharyngeoma, cysts…) **Injury** of CNS **Pituitary surgery/radiation** **Infection / infiltration** (meningitis, hemochromatosis, histiocytosis X and others)

ADRENAL INSUFFICIENCY SIGNS AND SYMPTOMS

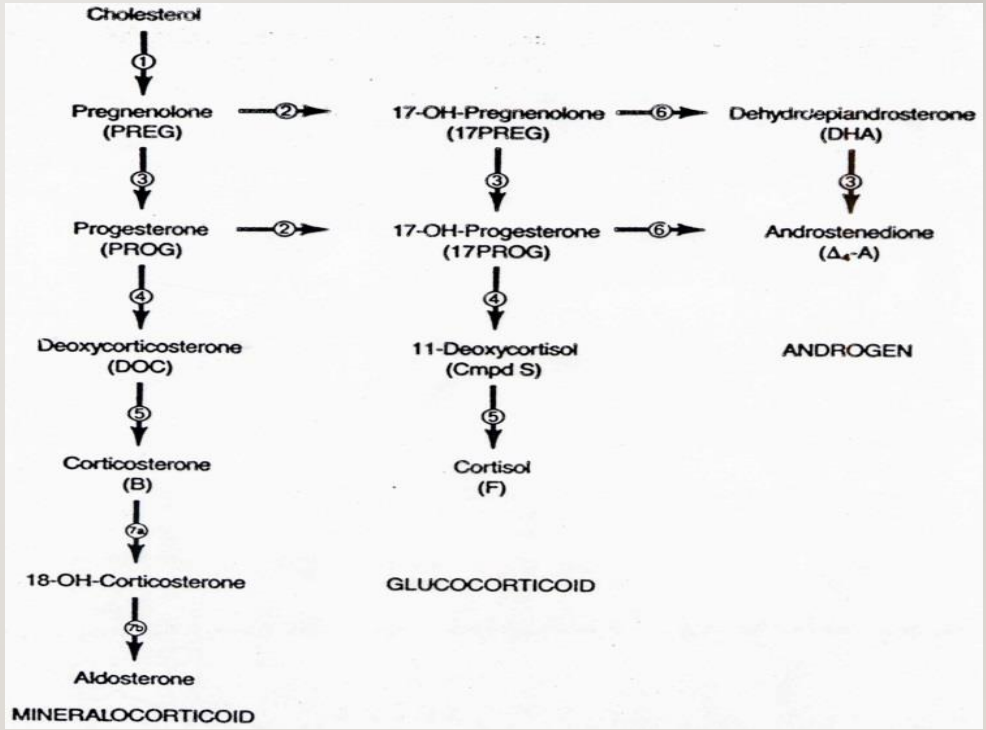
Signs and symptoms	Laboratory findings
Glucocorticoid deficiency	
Fatigue, weakness Loss of appetite, weight loss Nausea, vomiting Muscle pain	Hypoglycemia
Mineralocorticoid deficiency	
Muscle weakness Dehydration, weight loss Hypotension Salt craving	Hyponatremia, hyperkalemia, acidosis
Adrenal androgens deficiency	
Decreased pubic and axilar hair	
Elevated levels of ACTH	
Hyperpigmentation	

CONGENITAL ADRENAL HYPERPLASIA (CAH)

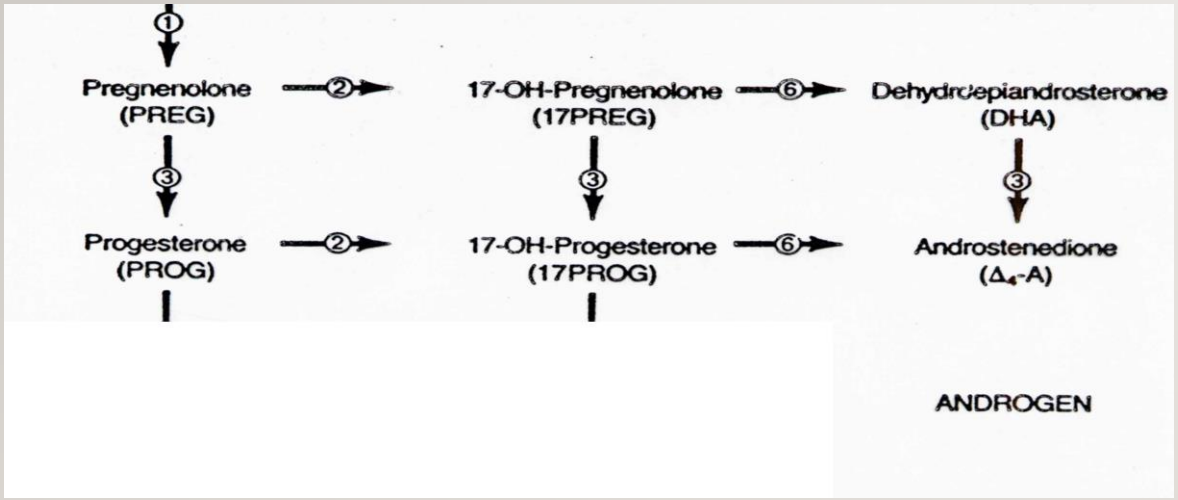
- AR inheritance, 6th chromosome, CYP21 gene
- Enzymatic defect of adrenal steroidogenesis

- **<u>Europe 1: 10 000 – 1: 15 000, CR 1: 12 000</u>**
- (Eskimos in Alaska 1: 280)

- 21 hydroxylase deficiency > 90%
- 11 hydroxylase deficiency 5%
- 3 β hydroxylase deficiency < 2%



CAH- 21-HYDROXYLASE DEFICIENCY



↓ gluco- and mineralocorticoids levels

↑ androgens levels (↑ precursors above the „block“)

Forms

salt wasting (SW) – 75%

simple virilizing (SV) – 25%

nonclassic (NC)

late-onset (LO)

SALT -WASTING CAH

- **Signs and symptoms:**
- *girls – virilisation of external genitalia*
- *(*fetal life ↑ androgens levels) → examination and therapy
- *boys – normal external genitalia*
- *salt -wasting crisis (gluco a mineralocorticoid deficiency)*
- manifestation 4th-14th day of life (up to 3 months)
- vomiting, failure to thrive, lethargy, dehydration, hypotension
- …. Sudden death

SIMPLE VIRILIZING CAH

- pseudopubertas praecox
- at the age of 2 - 4 years
- accelerated growth velocity
- advanced bone age
- precocious secondary sexual characteristics development (pubarche, prepubertal testicular volume)
- precocious epiphyseal closure - reduced final height compared to prediction

CAH - LABORATORY FINDINGS

- **In time of crisis**
- ↓ cortisol, aldosteron levels
- hyponatremia, hyperkalemia, hypoglycemia
- ↑ ACTH levels
- ↑ **17-hydroxyprogesteron levels**
- ↑androstendion, testosteron
- **Out of crisis, in unclear cases** - ACTH dynamic test

CAH – NEONATAL SCREENING

- studies in Canada and MESPE
- up to 25% of boys with SW-CAH may die due to misdiagnosis
- **17-hydroxyprogesteron**e from dry drop - "**cut off" 90 nmol / l**
- **100% sensitivity for SW**
- up to 1/3 SV remains unrecognized !!!

CAH – TREATMENT GOALS

- Prevention of adrenal insufficiency
- Ensuring normal growth and puberty
- Ensuring normal sexual life and fertility
- Genetic counseling
- Treatment -hormonal substitution
- genital reconstruction surgery
- genetic counseling

CAH -THERAPY

- **Substitution-suppression treatment**
- 1. **Glucocorticoids**
- Hydrocortison 8-12 (20) mg/m2 divided to 3 equal doses

- **2. Mineralocorticoids** -Fludrokortison 0,15 - 0,2 mg/m2

- 3. NaCl 2-3 g daily

CAH – TREATMENT CONTROL

- S-17 OHP, Na, K
- PRA
- ACTH
- Androstendion, Testosteron
- Growth velocity
- Secondary sexual characteristics
- Bone age

CAH – SURGERY

- **Genital reconstruction surgery - feminizing genitoplasty**
- 1. Initial surgery at the age of 2-3 years (toddler age)
- 2. Further surgery at the age of 12-14 years, if necessary
- Surgery not necessary for mild virilization
- Recommended for severe virilization (Prader> 3)
- Low-fitting vaginal orifice - clearly
- Highly open vagina - age of surgery is questionable (length of studies, change of surgical procedures, comparison of complications, results…)

- *Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP.* ***Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline.*** *J Clin Endocrinol Metab. Sep 2010;95(9):4133-60. [Medline].*

CAH –GENETIC COUNSELING

- **Parents – further pregnancy**
- *Prenatal diagnostics*
- **Molecular genetics** – chorionic villi, mutations of the CYP 21 gene
- ***Possible Solution***
- Termination of pregnancy
- Prenatal treatment - still experimental
- **Child - in a future partnership**

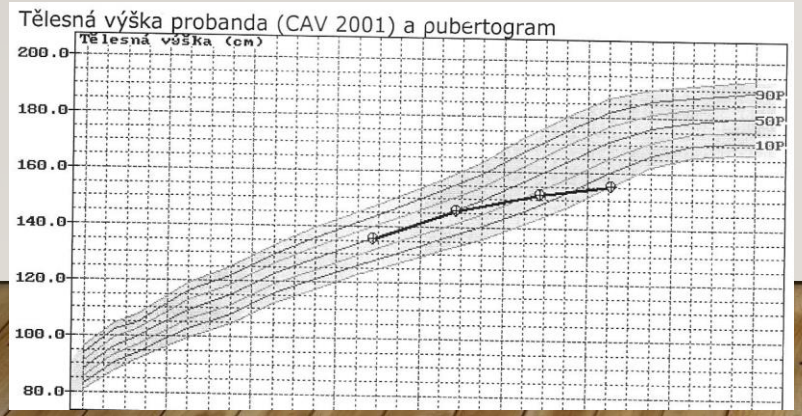
GLUCOCORTICOID OVERPRODUCTION CUSHING SYNDROME/DISEASE

Secondary (central) Cushing disease	**Pituitary adenoma** The most common cause of endogenous overproduction in children > 7 years
Primary (Cushing syndrome)	**Exogenous** - glucocorticoids administration **Endogenous** – adrenal cortex tumor

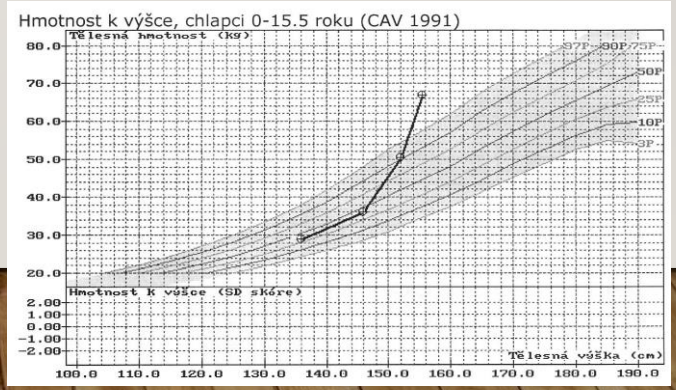
GLUCOCORTICOID OVERPRODUCTION CUSHING SYNDROME/DISEASE

- **Signs and symptoms**
- **central obesity and growth retardation**
- behavioral changes, emotional lability of depression
- weakness
- „moon“ face
- Hypertrichosis
- hypertension
- Striae, skin atrophy, bruises
- Osteoporosis
- Hyperglycemia
- Menstrual cycle disorders

Tělesná výška probanda (CAV 2001) a pubertogram



Hmotnost k výšce, chlapci 0-15.5 roku (CAV 1991)



GLUCOCORTICOID OVERPRODUCTION LABORATORY TESTS

- 24-hour urine collection - free kortisol
- Loss of diurnal rhythm - serum cortisol in the morning and midnight
- Dexamethason suppression test (short x long, low dosed x high dosed, combinations)