Paediatric metabolic medicine

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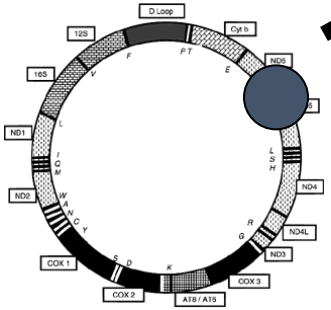
State-exam-qs-special Pedi

Disorders of amino acids metabolism
Disorders of lipid metabolism
Disorders of carbohydrate metabolism
Lysosomal disorders

Neonatal screening, breast feeding (contraindication)
Hepatomegaly
Splenomegaly
Hypoglycemia
Developmental delay
Hypotonia of neonate and infant
Neuromuscular disorders
Disease of the liver
Cardiomyopathy
Epilepsy
Blood-gas and acidobasic status analyses

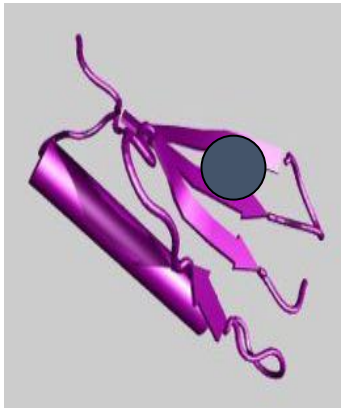
Metabolic medicine

Genome



23 000 genes (nDNA)
37 genes (mtDNA)

Proteome



protein

>900 000
>2000
enzymes

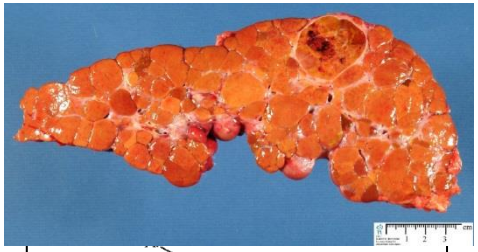
Metabolome

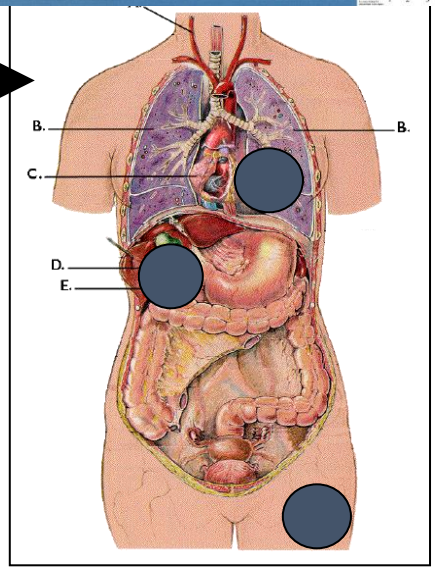
substrat

product

Substances urine 4 000
Substances blood 4 600
Substances CSF 440

Organome





Phenotype >6000
Genotype >4000

IEMbase©

Inborn Errors of Metabolism Knowledgebase

Inborn Errors of Metabolism Knowledgebase

Diagnosis

- Range of searches
- Complex searches
- Detailed report

Search technologies by University of British Columbia

News / Updates

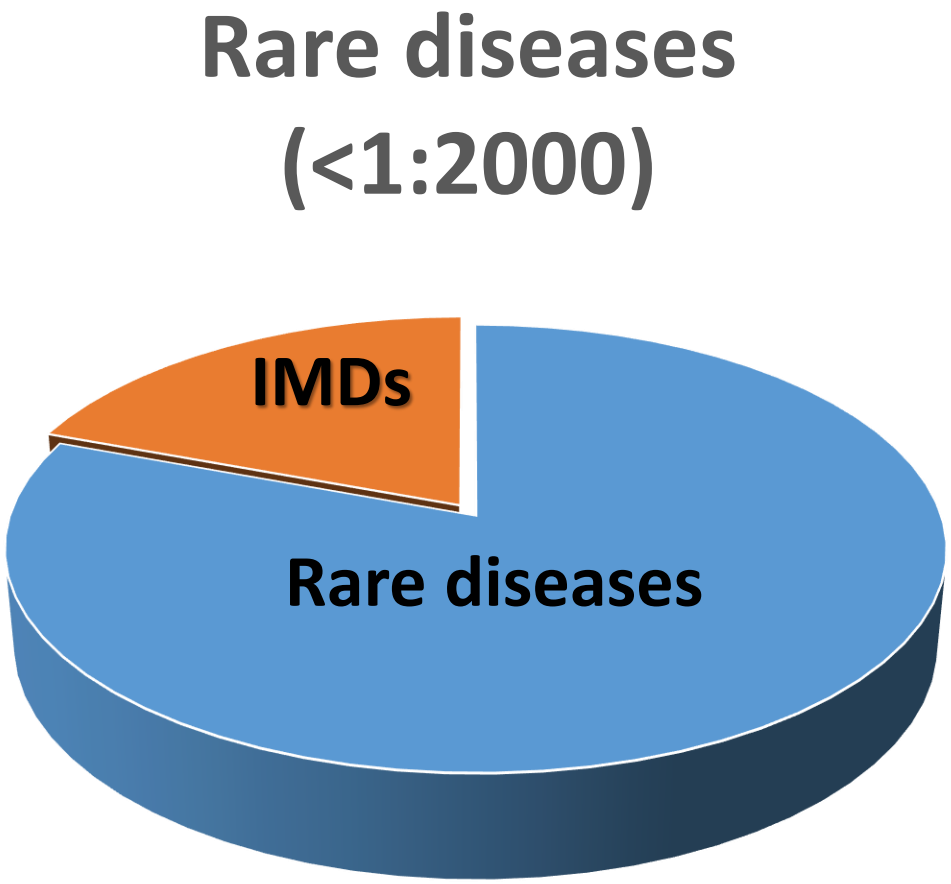
Current number of diseases

18.09.2023 - 1882

Diseases added

18.09.2023 - COG3-CDG
05.08.2023 - MAN2A2-CDG
07.07.2023 - Syntaxin 1A deficiency (STX1A)
02.06.2023 - 3-hydroxy-3-methylglutaryl-CoA reductase deficiency (HMGCR)
25.05.2023 - Serine palmitoyltransferase, small subunit A deficiency (SPTSSA)
29.04.2023 - Phosphoadenosine 5'-phosphosulfate transporter deficiency

Inherited metabolic disorders



IMDs ~ 1/3 rare diseases

Prevalence
1:80-120 (without FH 1:500)

General paediatrician
3-5 patiens with IMDs

Metabolic derangement

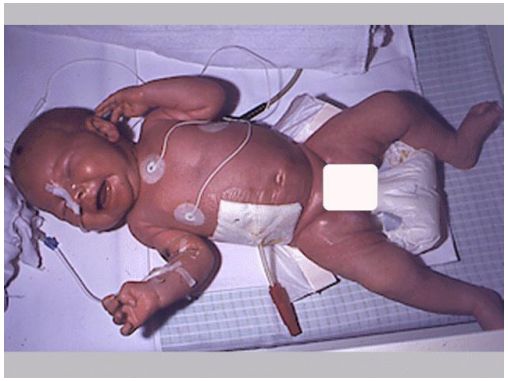
IMDs which give rise to intoxication
(Urea cycle, organic acidurias)

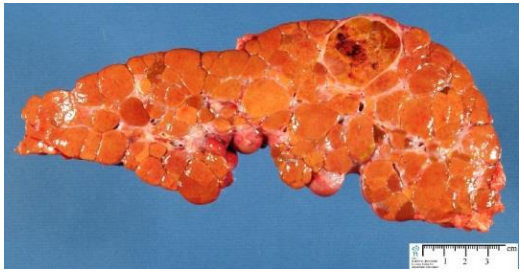
Substrate accumulation

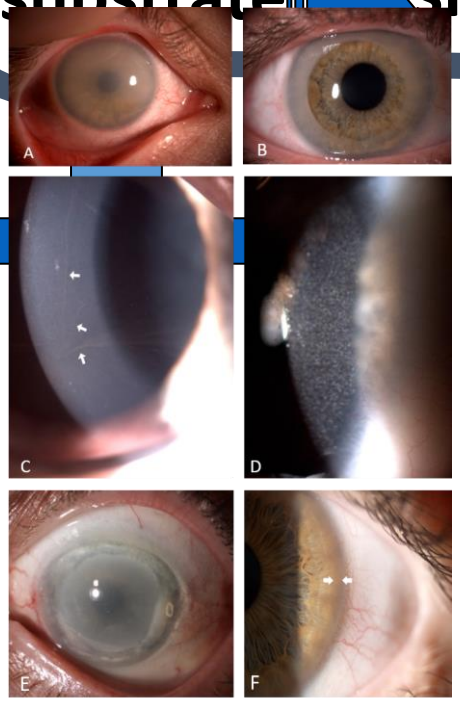
Complex molecules
(lysosomal storage)

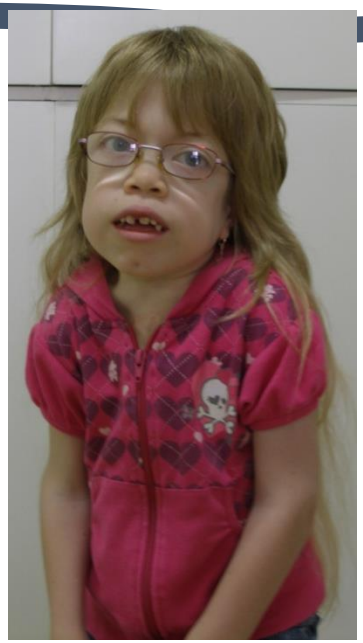
prekursor

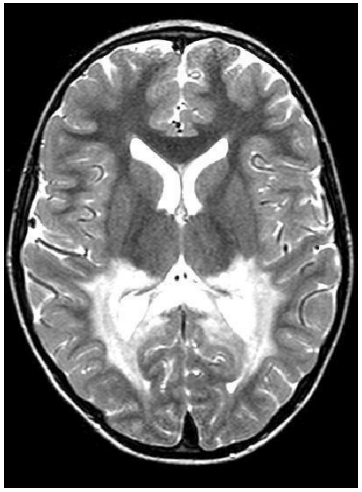
substrate → **side product**







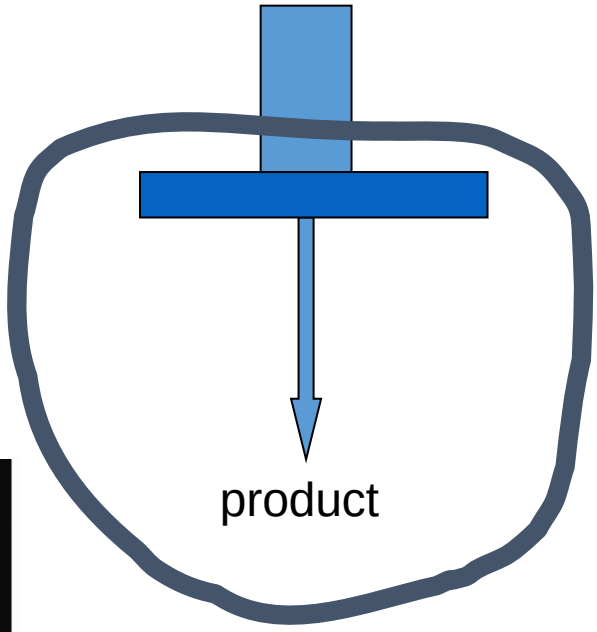




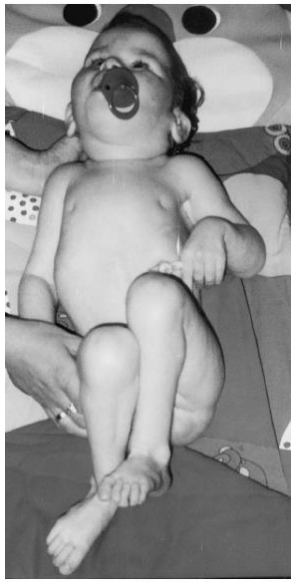
Metabolic derangement

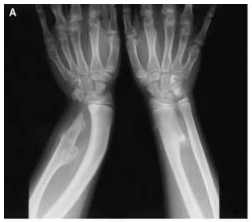
Signals and trafficking (glycosylation disorders)

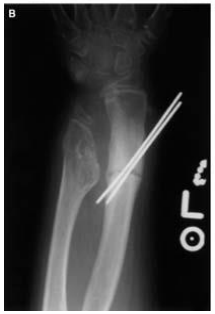
Lack of products

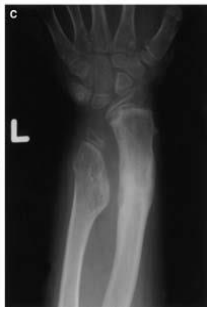


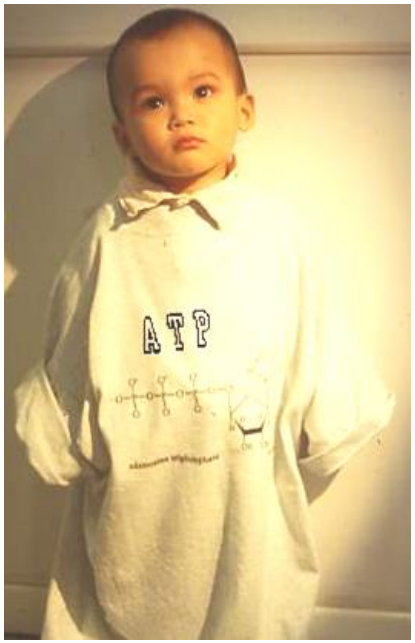
Energy failure (mitochondrial disorders)











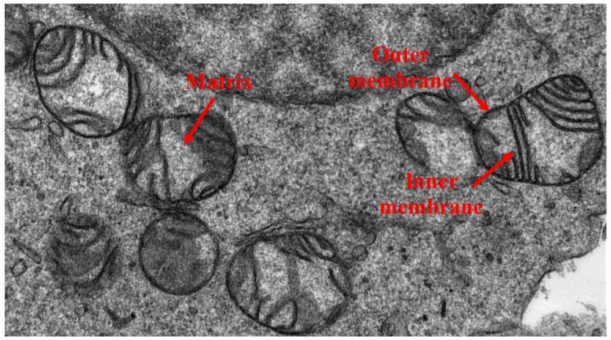
Inheritance of IMD

autosomálně recesivní	fenylketonurie (PKU) glutarová acidurie typu I (GA) homocystinurie z poruchy cystathionin-β-syntázy (CBS) neonatální encefalokardiomyopatie s 3-methylglutakonovou acidurií a poruchou proteinu TMEM70 deficit fosfomanomutázy 2 (PMM2-CDG) Pompeho nemoc (glykogenóza typu II) syndrom Hurlerové (MPS typu I) Zellwegerův syndrom
autosomálně dominantní	GLUT1 deficit (glukózový transportér 1) atrofie optiku – OPA1 akutní intermitentní porfyrie Kufsova nemoc (NCL) AD deficit GTP cyklohydrolázy-I CADASIL
vázaná na chromosom X	porucha ornitintranskarbamylázy (OTC) X-vázaná adrenoleukodystrofie (X-ALD) Leschův–Nyhanův syndrom Menkesova nemoc Danonova nemoc Hunterův syndrom (MPS typu II) porucha PDH E1α deficit kreatinového transportéru Rettův syndrom
maternální dědičnost	NARP syndrom MELAS syndrom MERRF syndrom LHON syndrom maternálně dědičné poruchy sluchu maternálně dědičný diabetes a porucha sluchu (MIDD)
sporadický výskyt	Kearnsův–Sayreův syndrom Pearsonův syndrom

CADASIL = cerebrální autosomálně dominantní arteriopatie se subkortikálními infarkty a leukoencefalopatií; GTP = guanosintrifosfát; LHON = Leberova hereditární neuropatie optiku; MELAS = mitochondriální myopatie, encefalopatie, laktátová acidóza a iktu podobné příhody; MERRF = myoklonická epilepsie s RRF (ragged-red fibers); MPS = mukopolysacharidóza; NARP = neurogenní svalová slabost, ataxie a retinitis pigmentosa; NCL = neuronální ceroidlipofuscinóza; OPA1 = optická atrofie 1; PDH E1α = pyruvátdehydrogenáza, podjednotka E1α; TMEM70 = transmembránový protein 70

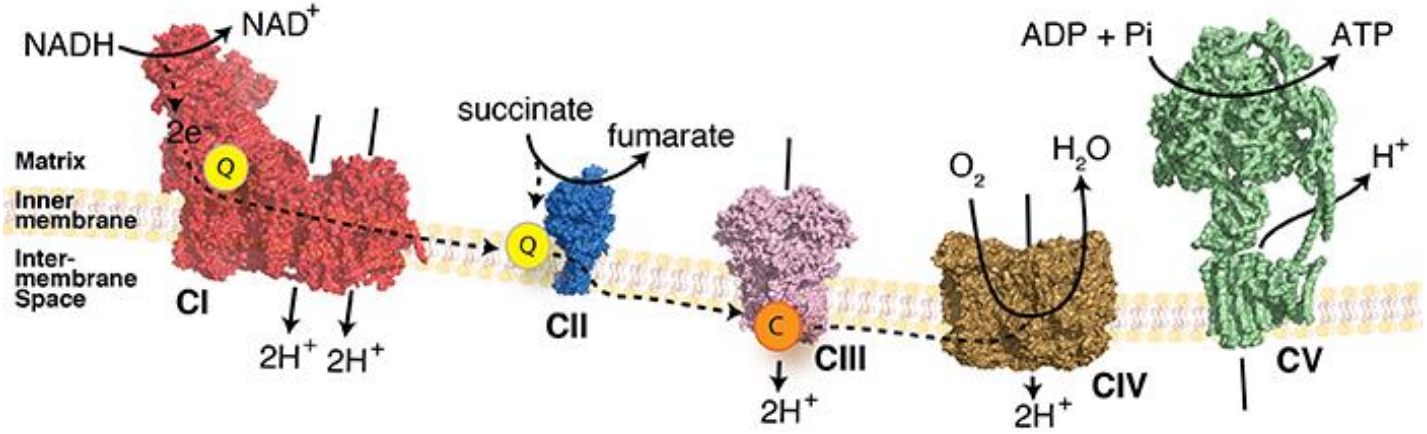
MENDELIAN INHERITANCE

MITOCHONDRIAL INHERITANCE



Honzík T a Zeman J. (2021)
Dětská Neurologie, Galen

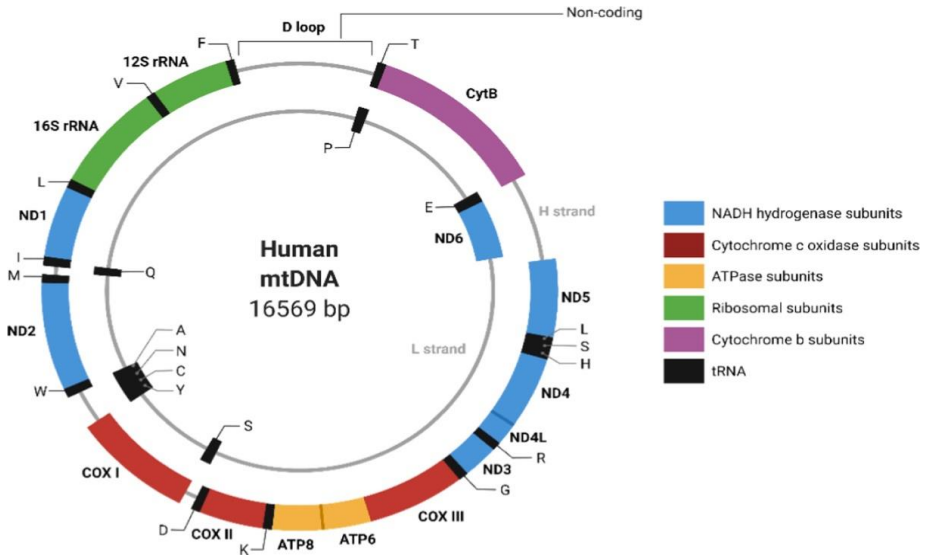
OXPHOS



Hock et al. (2020) *Biochem J*

	Enzyme	Mass (kDa)	Number of different types subunits	Number of mtDNA encoded subunits	Prosthetics groups
Complex I	*NADH dehydrogenase EC 1.6.5.3*	*~ 1000*	*44*	*7*	*FMN, 8 [Fe-S] clusters*
Complex II	*Succinate dehydrogenase EC 1.3.5.1*	*~ 140*	*4*	*0*	*FAD, 3 [Fe–S] clusters, heme b*
Complex III	*Cytochrome c oxidoreductase EC 1.10.2.2*	*~ 240*	*11*	*1*	*heme b and c1, 2 [Fe–S]*
Complex IV	*Cytochrome c oxidase EC 1.9.3.1*	*~ 200*	*14*	*3*	*heme a and a3, CuA, CuB*
Complex V	*ATP synthase EC 7.1.2.2*	*~ 650*	*18*	*2*	*-*

Vercellino and Sazanov (2022) *Nature*



Aldossary et al. (2022) *Saudi Pharm J*

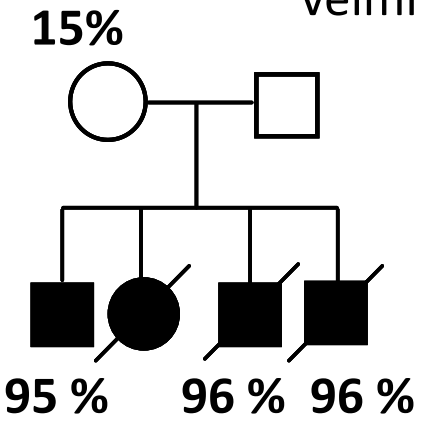
Mitochondrial inheritance

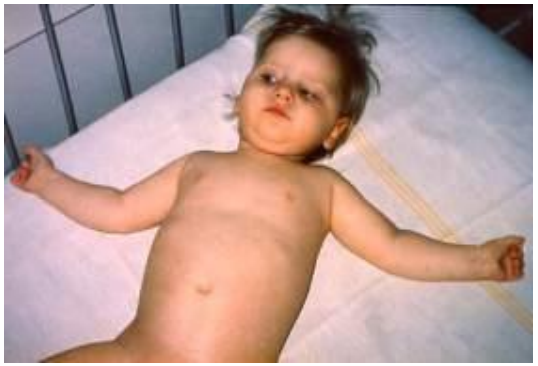
Rodokmen rodiny se syndromem **MELAS** na podkladě m.3243A>G v *MTTL1*

MILS/NARP syndrom

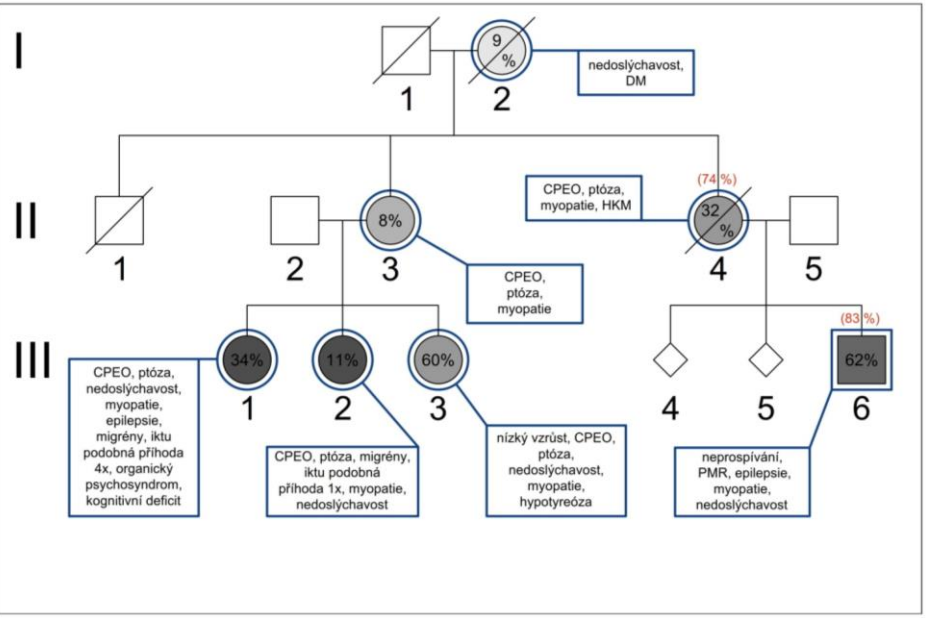
rodina s m.8993T>G v *MT-ATP6*

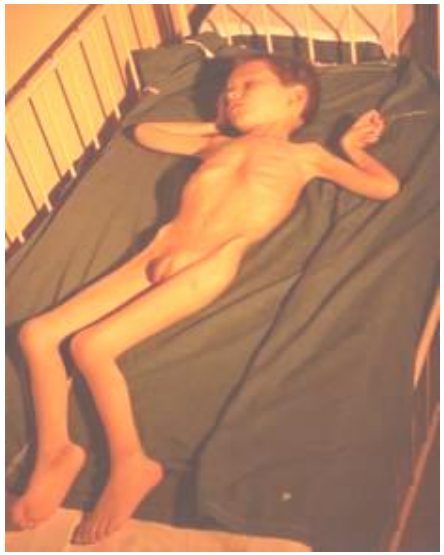
velmi heterogenní symptomy



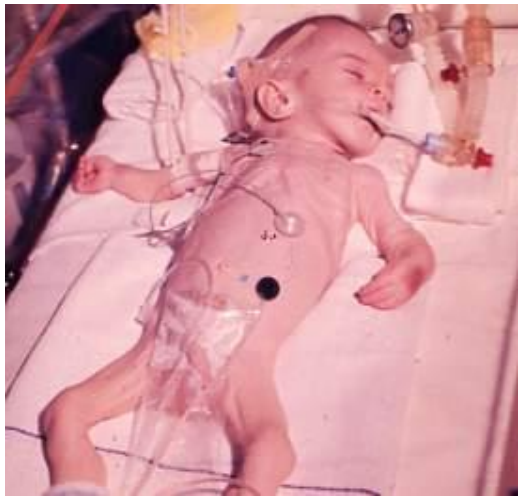


6 měsíců





8 let



3 měsíce

Disorders of Amino Acid metabolism

>135 hum genetic diseases,
in KPDPM dg. >1500 patients

What diseases?

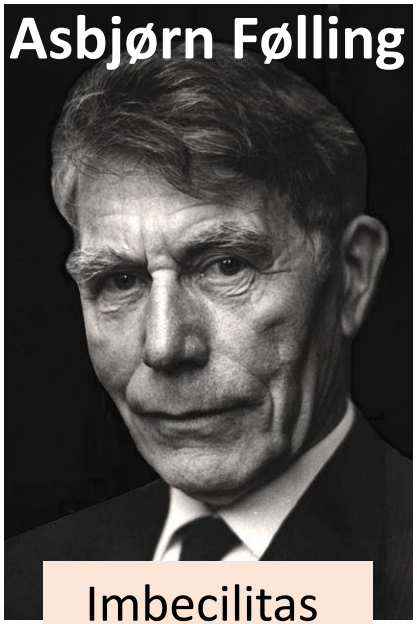
- ✓ **Hyperphenylalaninaemias, phenylketonuria**
- ✓ **Disorders of Tyrosine Metabolism**
- ✓ **Homocystinuria**

vitB12 def., folate def., classic homocystinuria

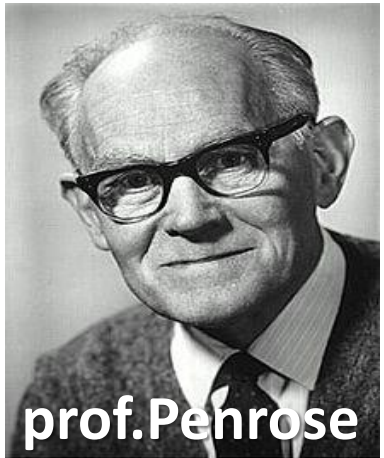
- ✓ **Urea Cycle disorders**

Phenylketonuria (PKU)

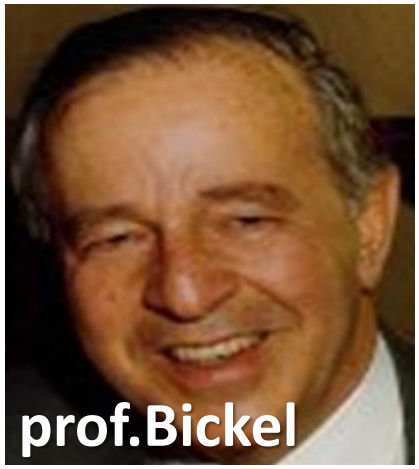
1934

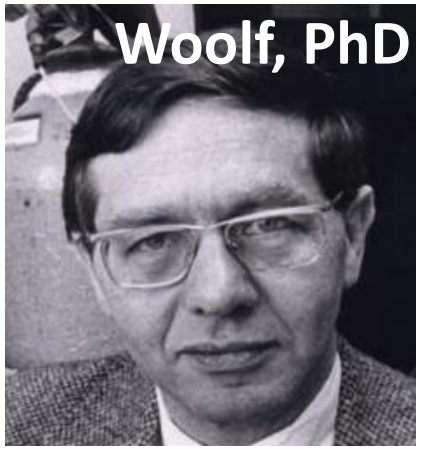


Imbecilitas fenylpyruvica



1958

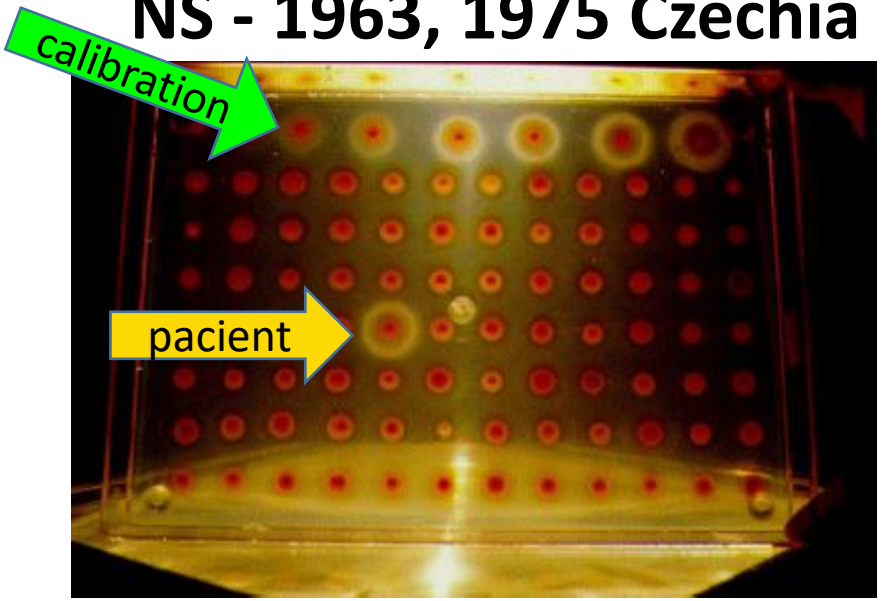




↓

Lofenalac

NS - 1963, 1975 Czechia



http://pkuworld.org/home/docs/history/guthrie200.jpg

- DBS
- Beta-2-thienylalanin in medium-growth inhibition *B. subtillis*
- ↑ Phe enable bacterial growth

Prof. Robert Guthrie 1916-1995
Pediatrics 1963

PKU – clinical features I

» progressive neurological impairment since early childhood

» intellectual disability (IQ <50)

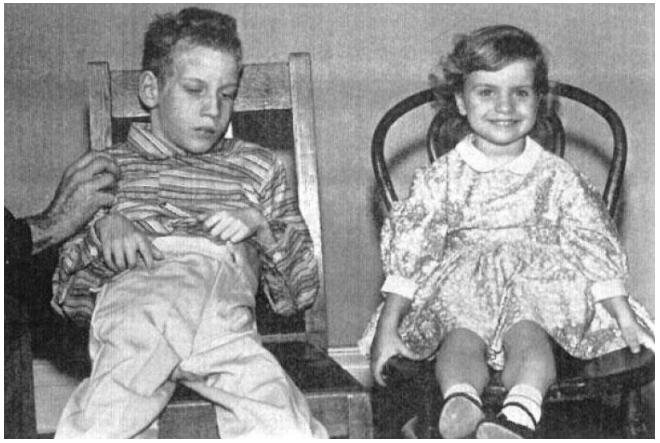
» microcephaly

» spasticity of the limbs

» parkinsonism

» gait disturbance

www.dshs.state.tx.us



www.phedup.co.uk

PKU – clinical features I

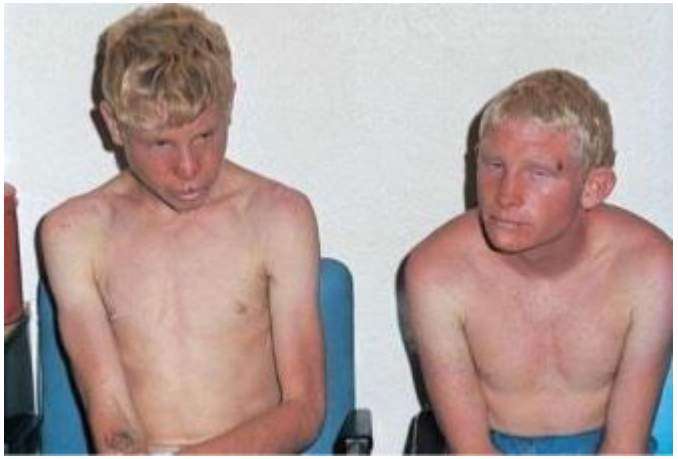
» mousey odour

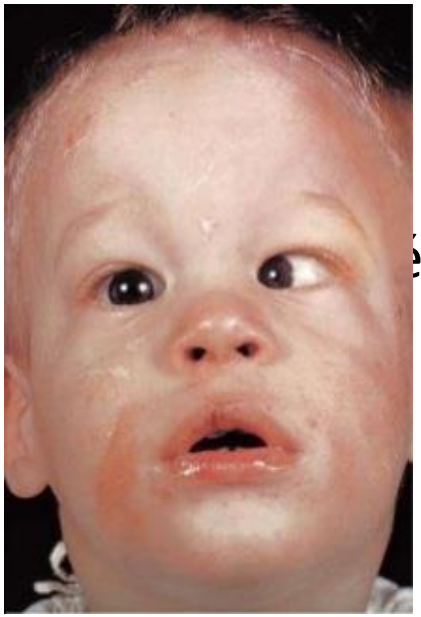
» eczema

» sparse and fair hair

» ↓ iris pigmentation

» stunted growth

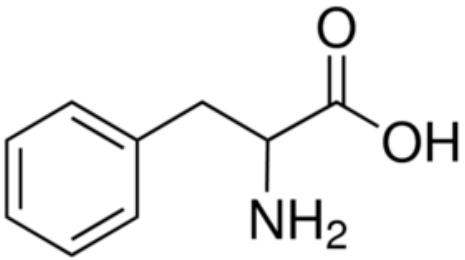




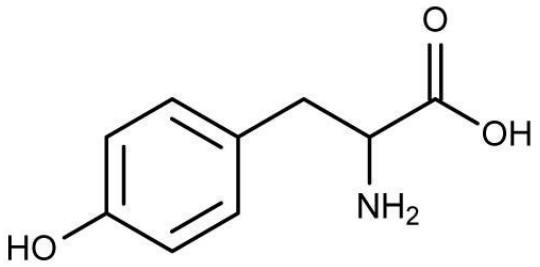
www.slideshare.net
www.faculty.ksu.edu.sa,
www.pkuacademy.org

Phenylalanine hydroxylase deficiency - PKU

phenylalanine



decrease of tyrosine



↓ **L-DOPA**

- Reduced skin, hair and iris pigmenation
- Photosensitivity
- Parkinsonisms
- Behviour problems
- Disturbed myelination

Phenylpyruvic acid - mousey odour

Phenyllactic acid

Phenylacetic acid - eczema

PKU - derangement

↑ blood Phenylalanine

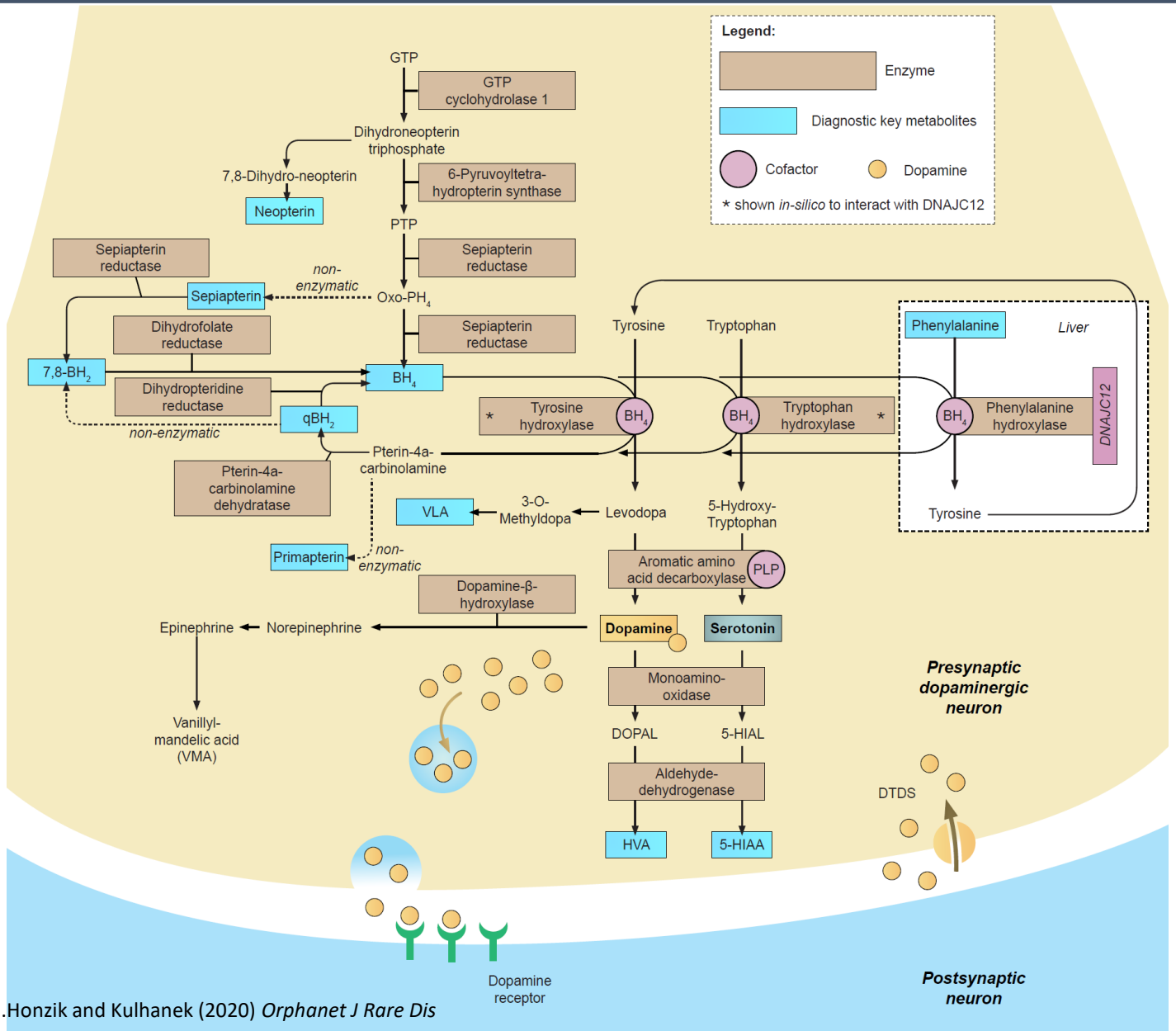
acetyl-CoA + acetoacetyl-CoA → HMG-CoA → mevalonic acid → ↓ cholesterol

↓ Myelin lipid synthesis in forebrain

www.msra.org.au

Impaired synaptogenesis, arborisation and disturbed myelination correlate with Phenylalanine levels

Malignant PKU - etiopatogenesis



Opladen..Honzik and Kulhanek (2020) *Orphanet J Rare Dis*

PKU – treatment

DIET FOR LIFE – restricted natural protein intake
Phe-free amino acid mixtures

Tolerance of Phe about one quarter
Phe 10-20mg/kg/day
Adults 600-900mg/day

Human milk has low Phe content (40mg/100ml)

PKU – diet/Phe in food

Food 100 g	P g	F g	C g	Energy kcal	Phenylalanine mg	Methionine mg
Eidam cheese (45% fat)	26	26	1,0	343	1370	614
lentil	24,3	1,2	60,3	319	1261	187
beef	22,3	1,3	-	101	912	613
chicken	20,5	6	-	136	852	573
pork	22,8	3,8	-	125	819	587
egg	12,5	11	0,9	151	728	403
croissant	11,4	1,4	73,1	351	518	163
rice	6,9	0,7	79,5	349	350	137
wafers/biscuit	5,4	15,0	75,5	449	220	40
cow milk	3,3	3,5	4,8	63	145	73
potatoes	2,8	0,2	20	98	86	25
human milk	1,2	3,1	7	67	47	22
grapefruit	0,6	0,2	10	40	16	6
apple	0,3	0,4	15	57	15	4
orange	0,7	0,2	20	84	12	3

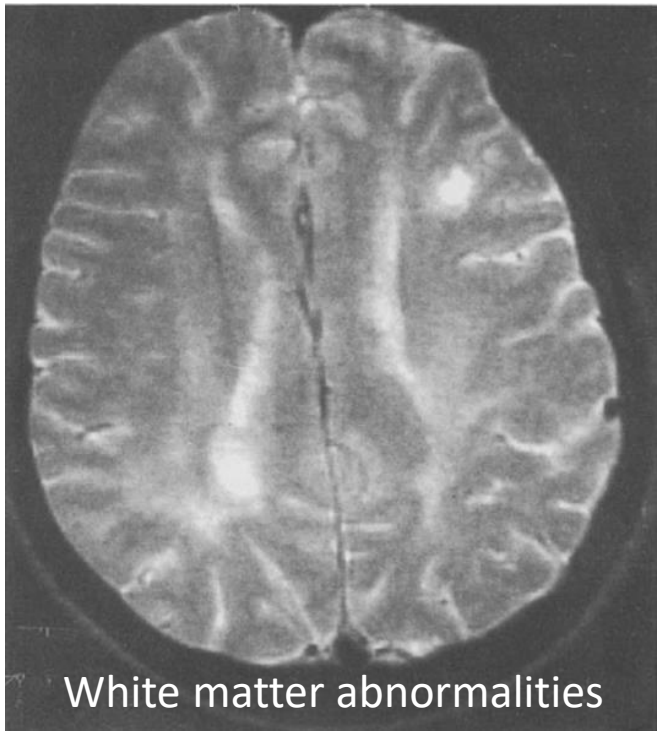
PKU – prognosis/outcome

If poor compliance

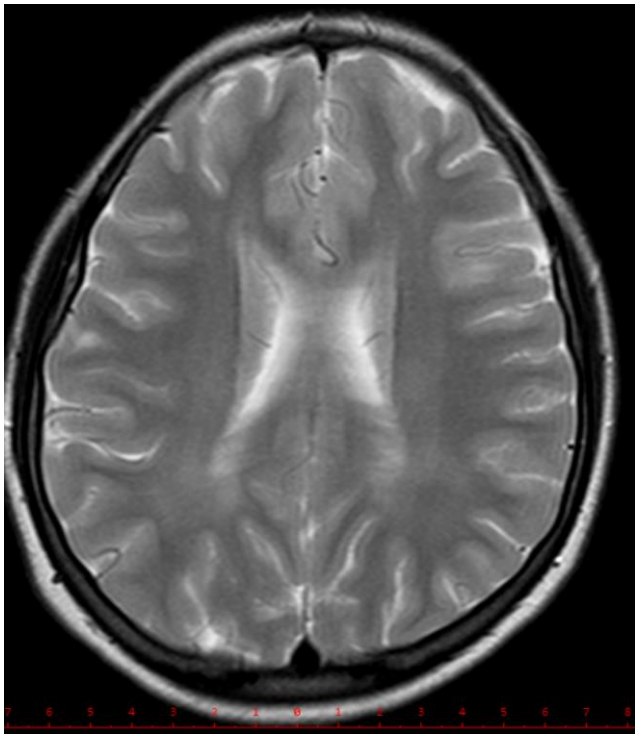
- ↓DQ/IQ

For each 300 µmol/l increase in blood Phe during the first 6yrs of life, IQ is reduced by 0.5 SD.

- Tremor, brisk reflexes
- Hyperactivity, temper tantrums, increased anxiety
- Depressive symptoms and low self-esteem



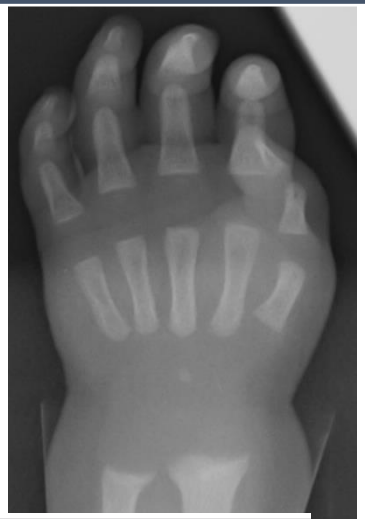
Villasana et al., 1989

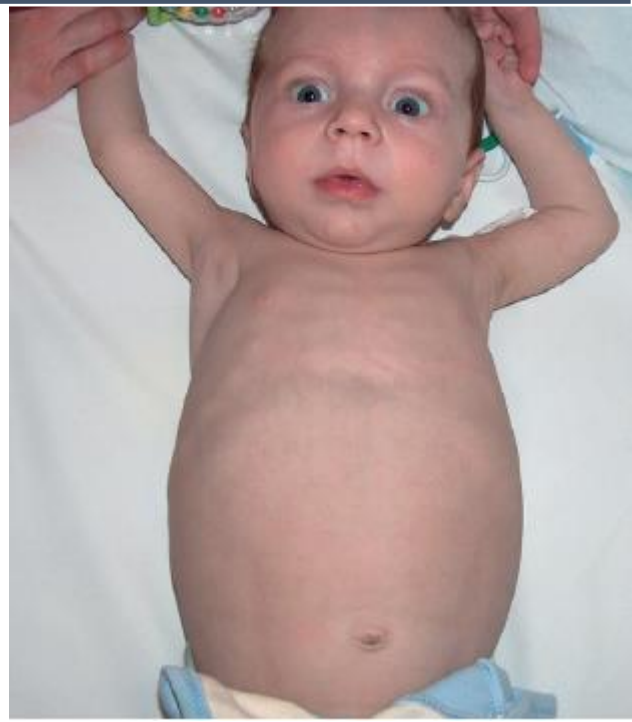


Our case

Tyrosinemia type 1

- since 3M of age
- distended abdomen
- hepatomegaly
- ascites
- rachitic rosary
- rickets on X-ray

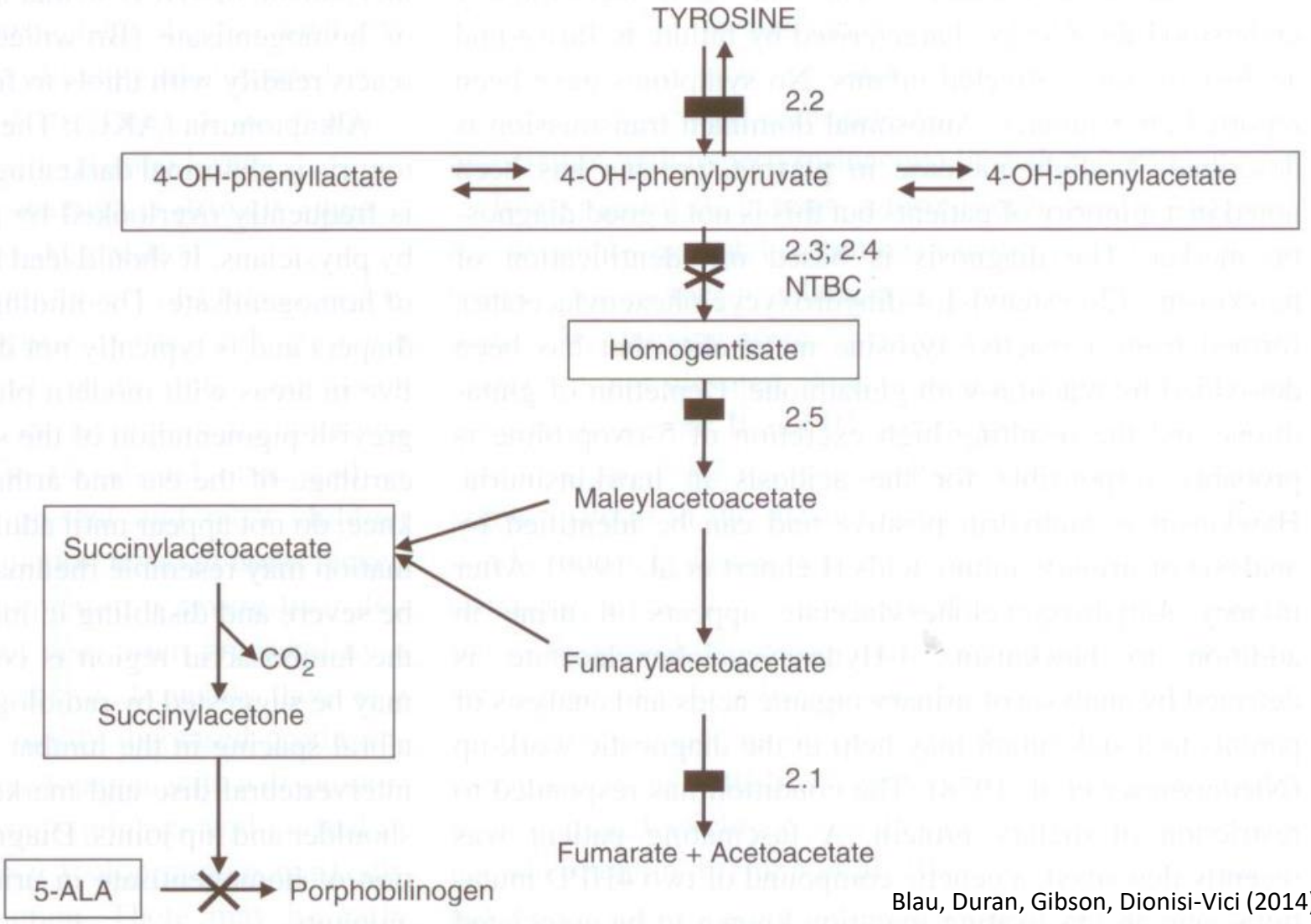




6M old boy

Vyšetření	Hodnota	Norma
ALT (μkat/l)	1,39	≤ 0,6
AST (μkat/l)	4,63	≤ 0,6
ALP (μkat/l)	22,07	≤ 6,2
INR	3,6	0,8–1,2
APTT (s)	78,4	≤ 40
Antitrombin III (%)	40	90–130 %
Protein C (%)	< 10	70–125 %
α_1-fetoprotein (μg/l)	150 000	≤ 8,1
Vápník v séru (mmol/l)	1,88	2,0–2,75
Fosfor v séru (mmol/l)	0,42	1,16–1,9
Tyrosin (μmol/l)	488	30–180
Sukcinylaceton v moči (μmol/l)	614	≤ 2
Kyselina δ-aminolevulová v moči (mmol/mol kreatininu)	103	nedetekováno

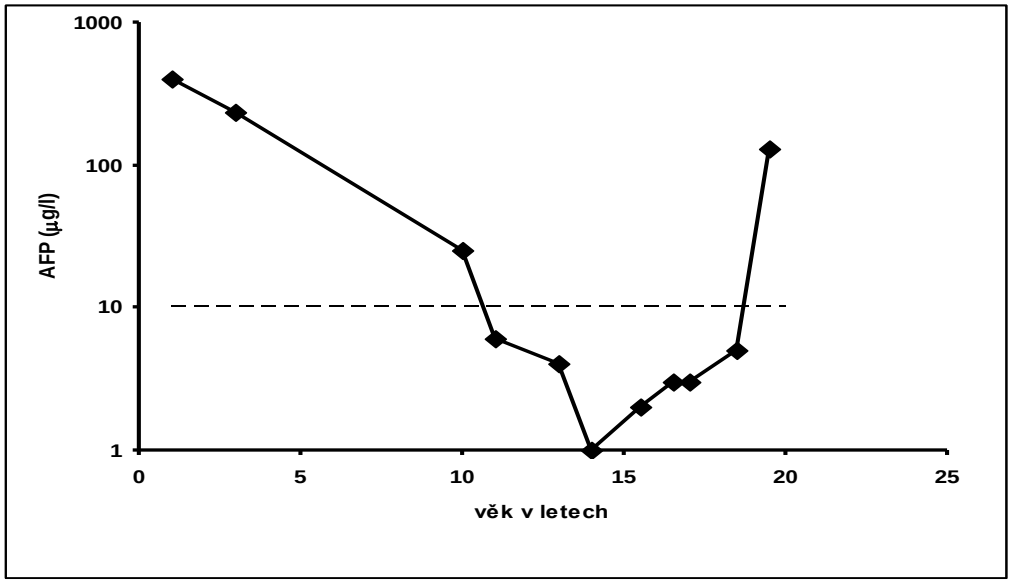
Tyrosinemia type 1

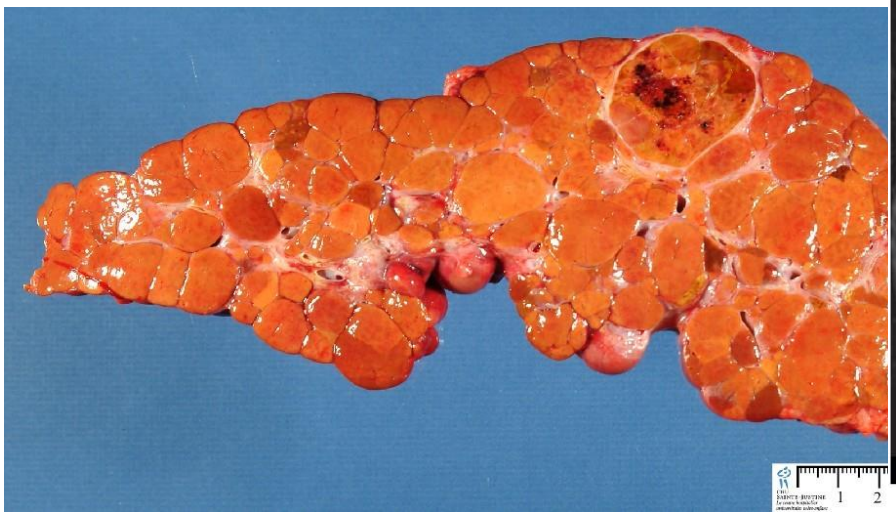


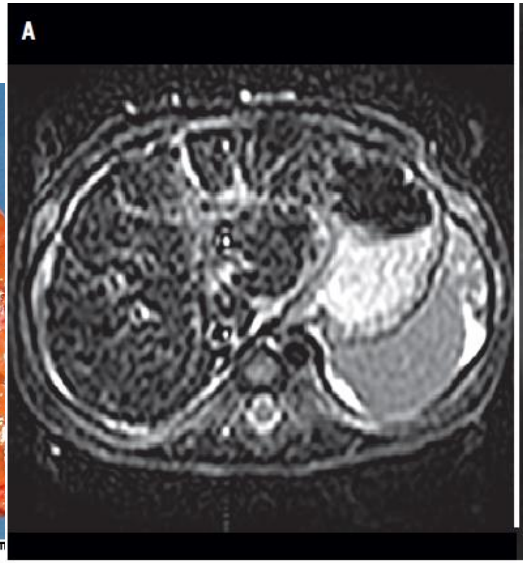
Blau, Duran, Gibson, Dionisi-Vici (2014)

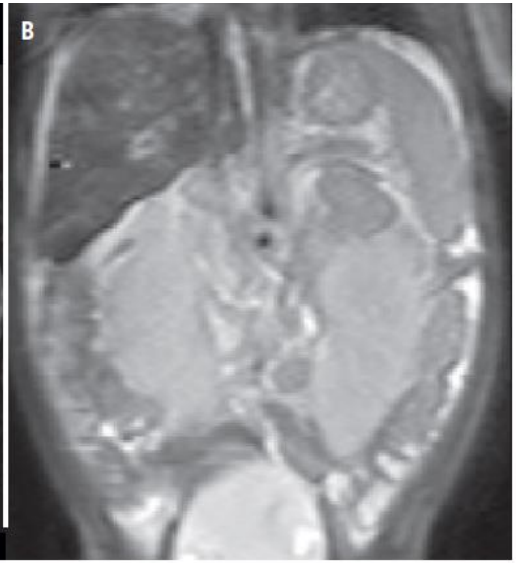
Tyrosinemia type 1

Long-term prognosis–
High risk of
HCC

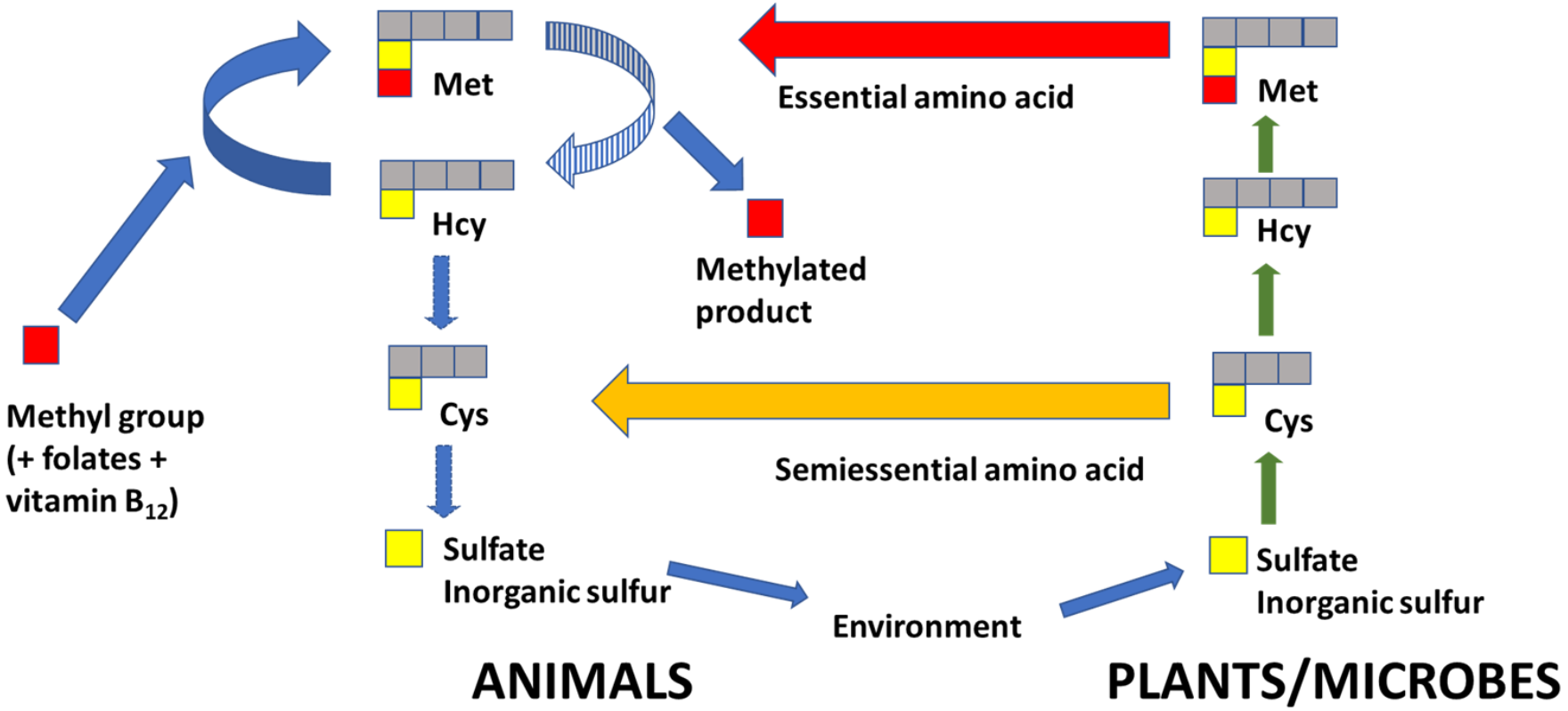




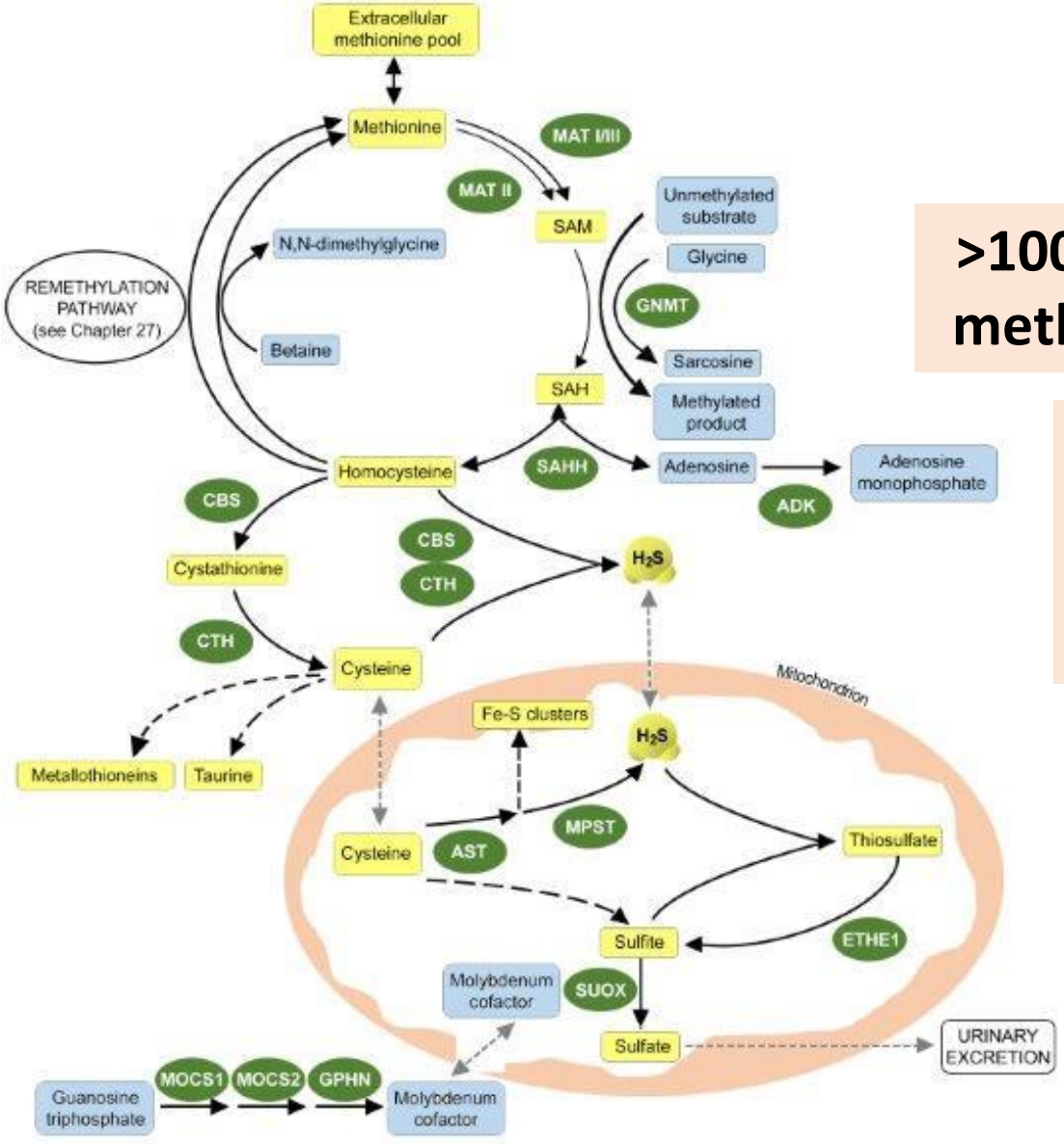




Metabolism of sulfur amino acids in nature



Metabolism of sulfur amino acids in human

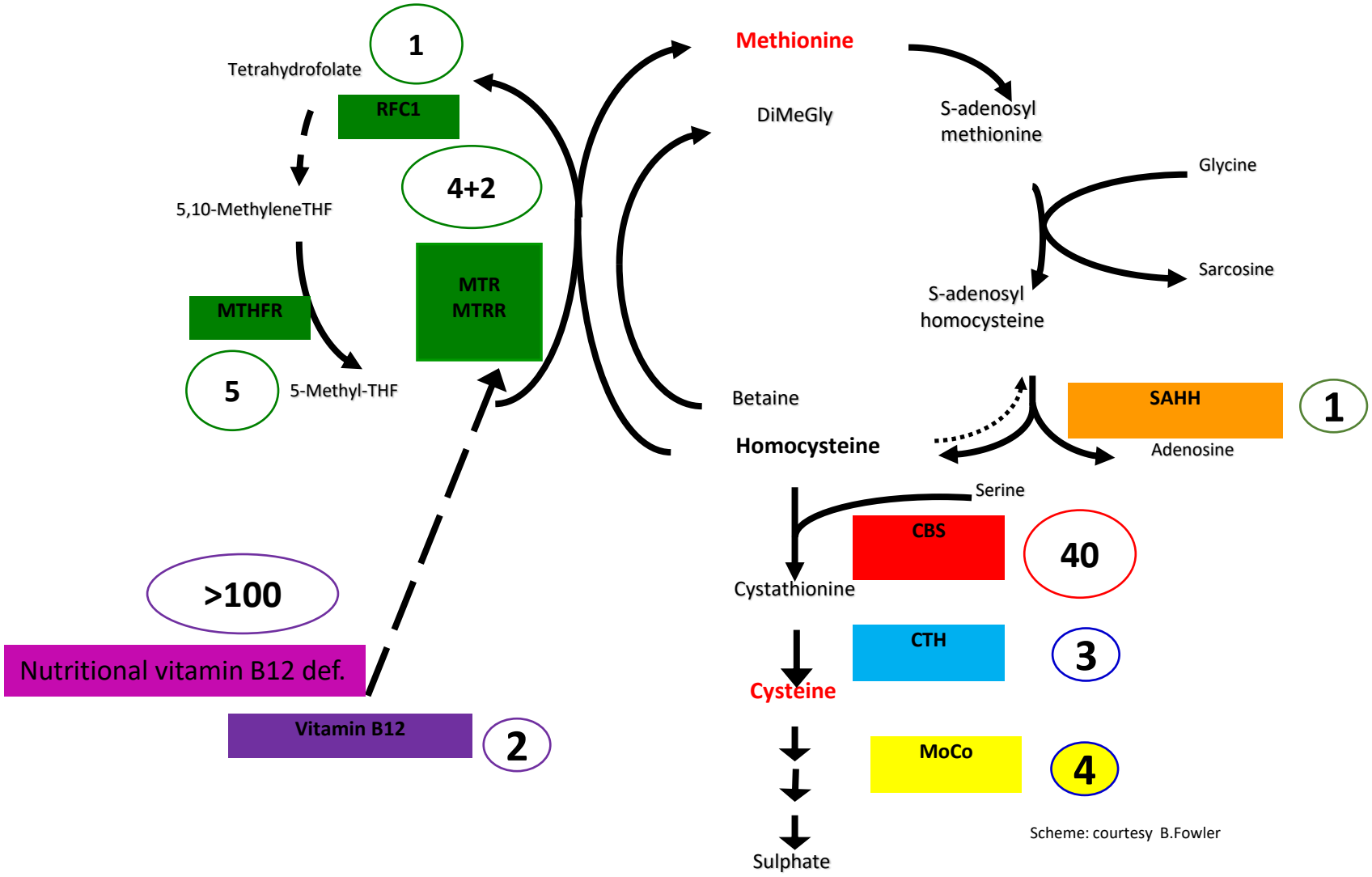


>100 SAM depend. methyltransferases

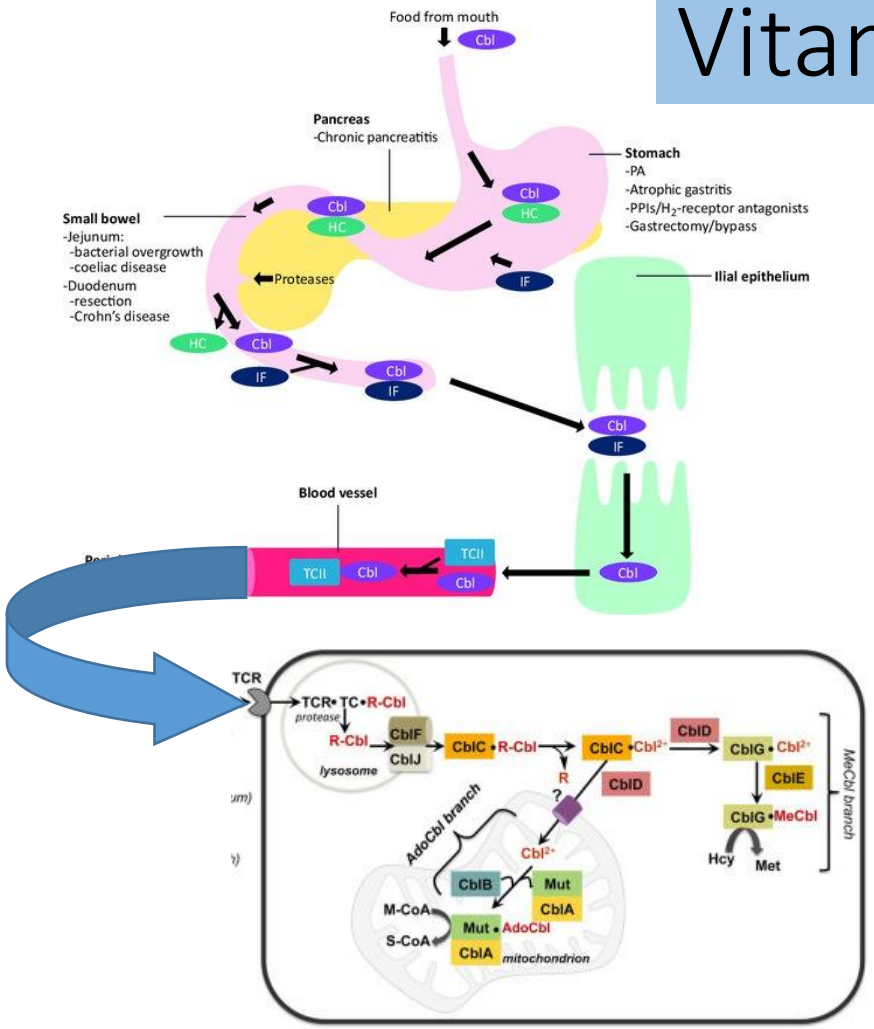
Phospholipids
Creatine
Neutrotransmiteres
DNA methylation
Myeline basic protein

Kozich, Morris, Blom, 2019

Pacients in the Czech Republic (2023)



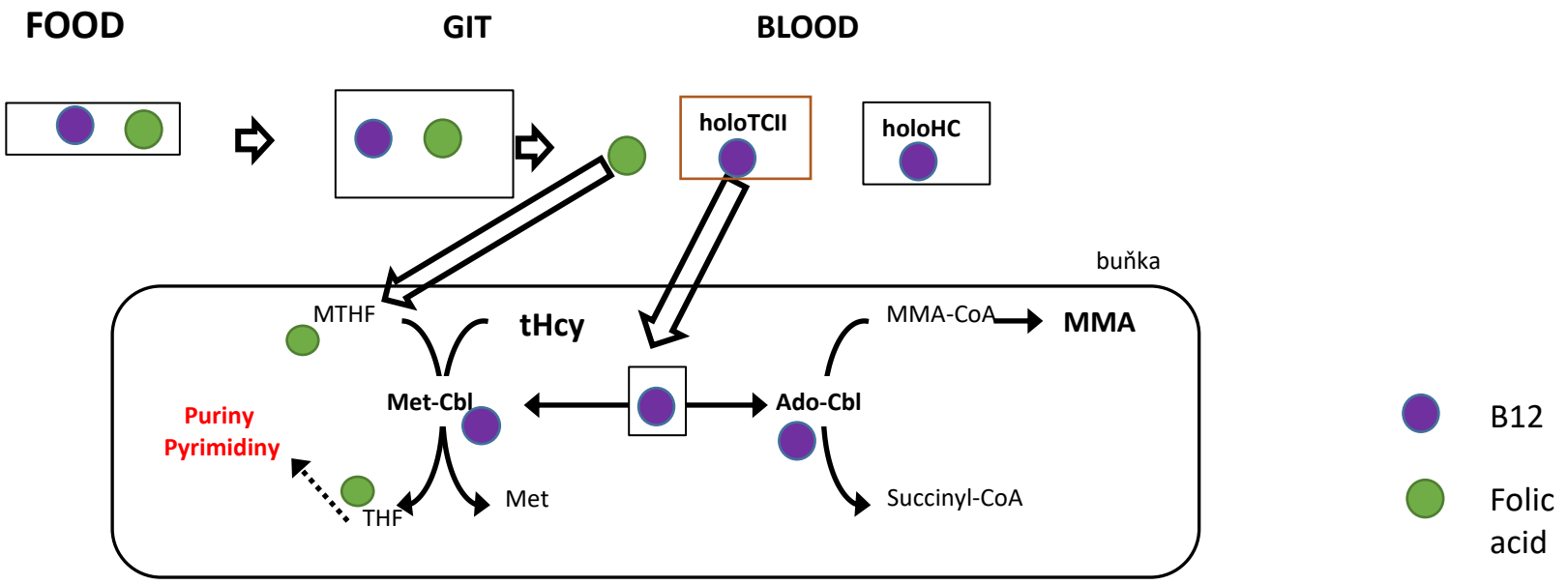
Vitamin B12



- Daily req 0.001-0.002 mg
- 2 enzymatic reaction
- Frequent endogenous and nutritional deficiency
  - Pregnancy and lactation
  - Elderly people
  - GIT dis.
  - Pernicious anemia
- Slow progression
  - anemia
  - dys/demyelination
  - Psychiatric disorders
- Therapy cheap and effective

https://www.researchgate.net/profile/Michael-Shipton-2
https://ars.els-cdn.com/content/image/1-s2.0-S0021925819545501-gr2.jpg

Cobalamin and folic acid interaction



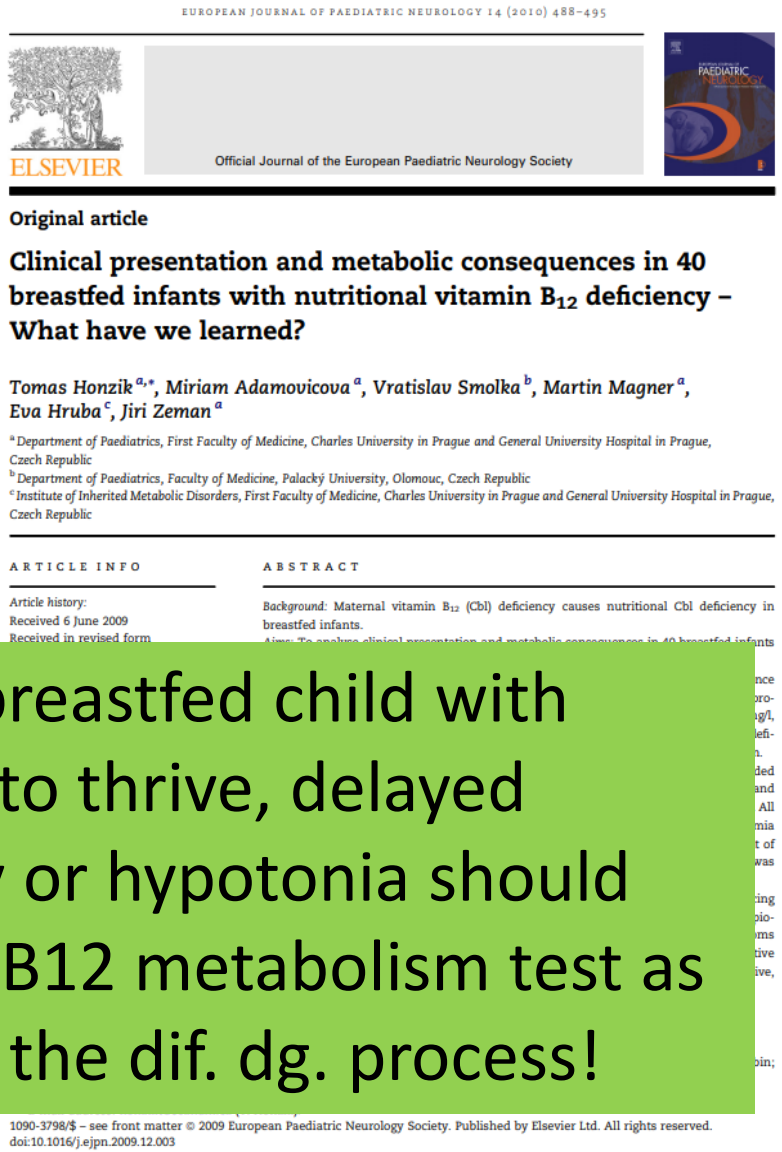
Nutritional vitamin B12 deficiencies in infants and toddlers

- 40 Cbl def. infants (2002-2006), 17 severe def.

- symptoms:

failure to thrive (48%), refusing breastfeeding (20%), vomiting (20%), hypotonia (40%), microcephaly (23%), delay PMDev (38%), regression of PMDev (28%), anemia 63% (megaloblastic 28%)

- Since then >30 infants



EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 14 (2010) 488–495

ELSEVIER

Official Journal of the European Paediatric Neurology Society

Original article

Clinical presentation and metabolic consequences in 40 breastfed infants with nutritional vitamin B_{12} deficiency – What have we learned?

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ABSTRACT

Background: Maternal vitamin B_{12} (Cbl) deficiency causes nutritional Cbl deficiency in breastfed infants.

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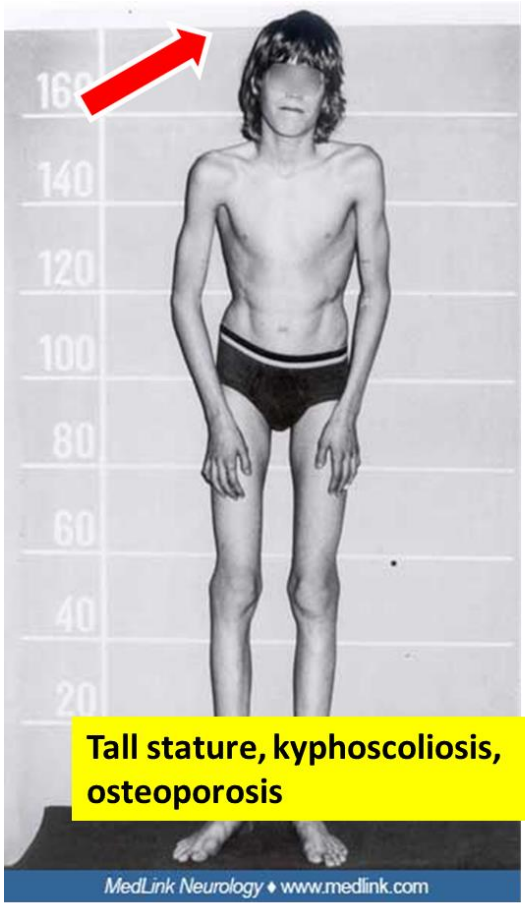
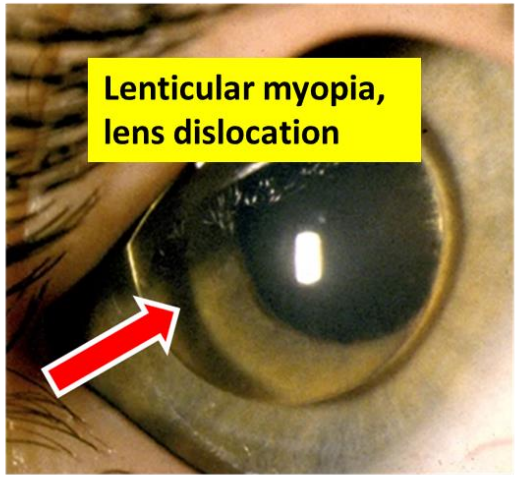
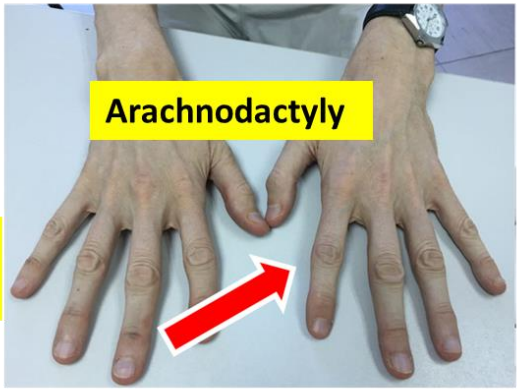
doi:10.1016/j.ejpn.2009.12.003

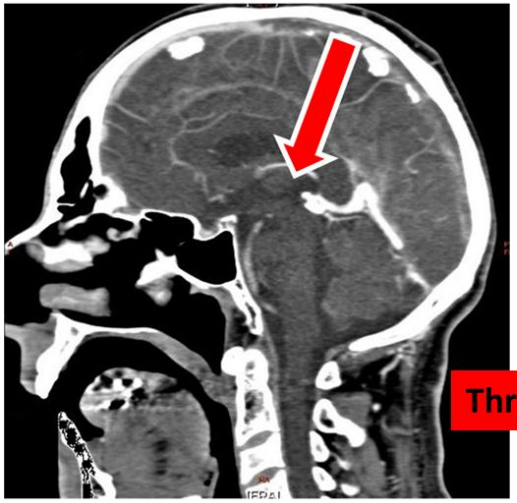
Every breastfed child with failure to thrive, delayed PMDev or hypotonia should have a B12 metabolism test as part of the dif. dg. process!

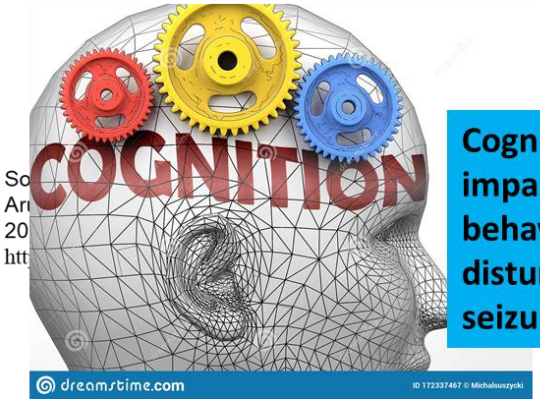
Typical clinical findings in CBS deficiency





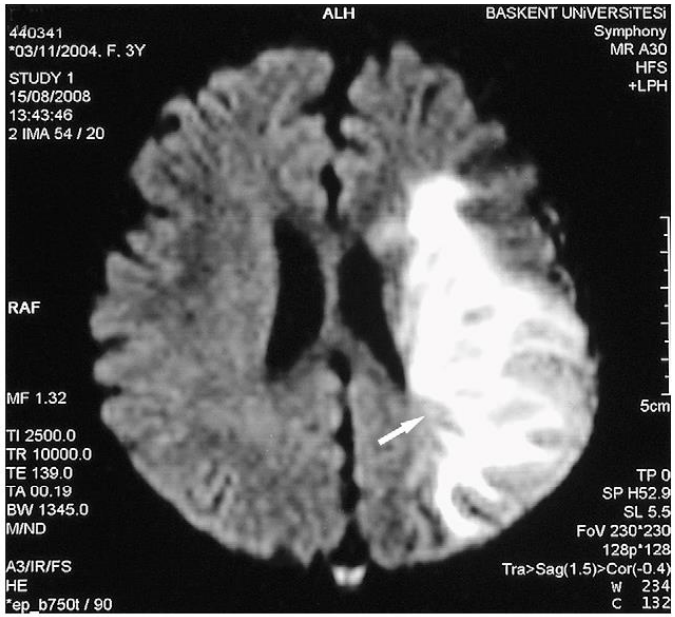


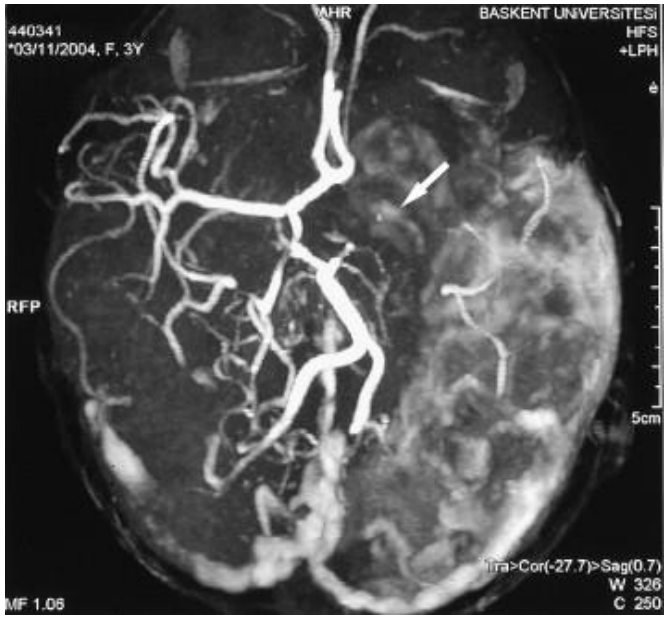




Cognitive impairment, behavioral disturbances, seizures

CBS deficiency - stroke





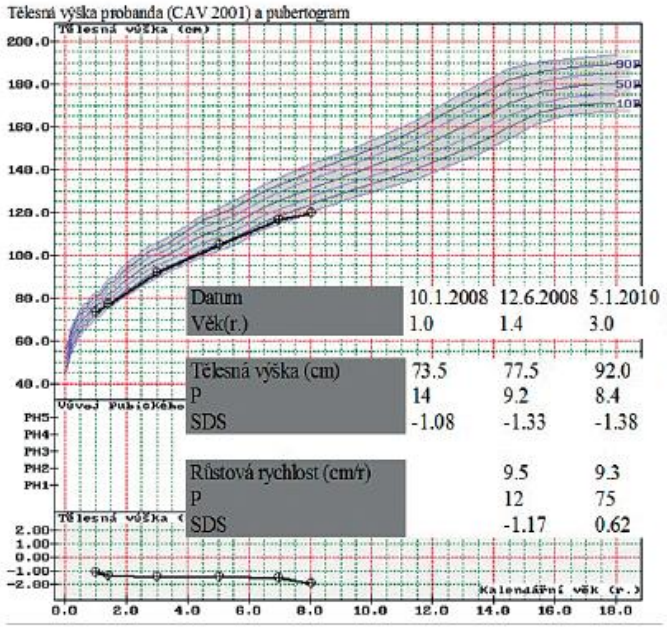
Failure to thrive, growth retardation

38+0
2150g, 44cm
(IUGR)

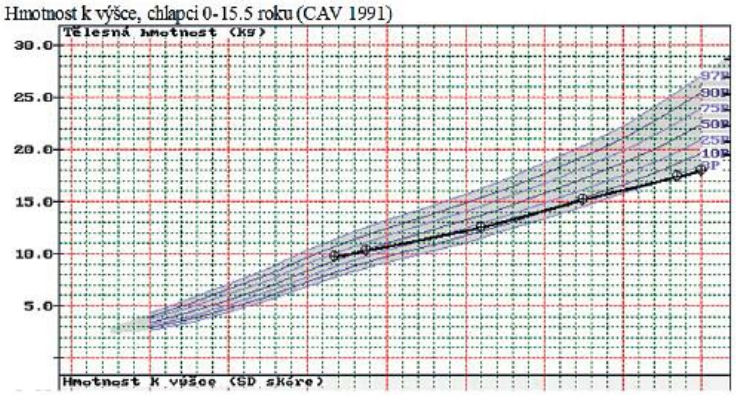
Cutch-up growth
Normal psychomotor dev

Rejection of meat, dairy desserts - cottage cheese, cream
Faltering growth
Physiological psychomotor development

0m	6m	12m	toddlerhood/preschool age



Datum	10.1.2008	12.6.2008	5.1.2010	25.1.2012	2.1.2014	29.1.2015
Věk(r.)	1.0	1.4	3.0	5.1	7.0	8.1
Tělesná výška (cm)	73.5	77.5	92.0	105.0	117.0	120.0
P	14	9.2	8.4	8.1	6.9	2.7
SDS	-1.08	-1.33	-1.38	-1.40	-1.48	-1.92
Růstová rychlost (cm/r)		9.5	9.3	6.3	6.2	2.8
P		12	75	50	55	<0.1
SDS		-1.17	0.62	0.01	0.11	-3.83

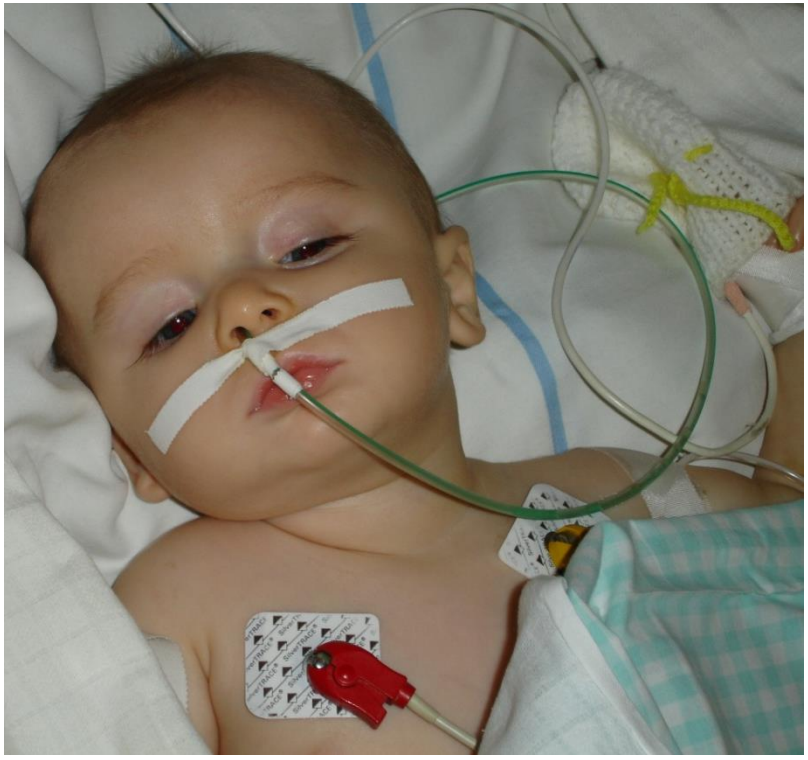


Datum	10.1.2008	12.6.2008	5.1.2010	25.1.2012	2.1.2014	29.1.2015
Věk(r.)	1.0	1.4	3.0	5.1	7.0	8.1
Tělesná hmotnost (kg)	9.8	10.4	12.6	15.2	17.4	18.0
P	30	19	6.7	4.9	2.2	1.0
SDS	-0.46	-0.87	-1.50	-1.65	-2.01	-2.31
Percentil hmotnosti k výšce	65	50	19	8.5	2.3	1.5
SDS hmotnosti k výšce	0.42	0.00	-0.90	-1.37	-2.00	-2.17

Urea cycle disorders

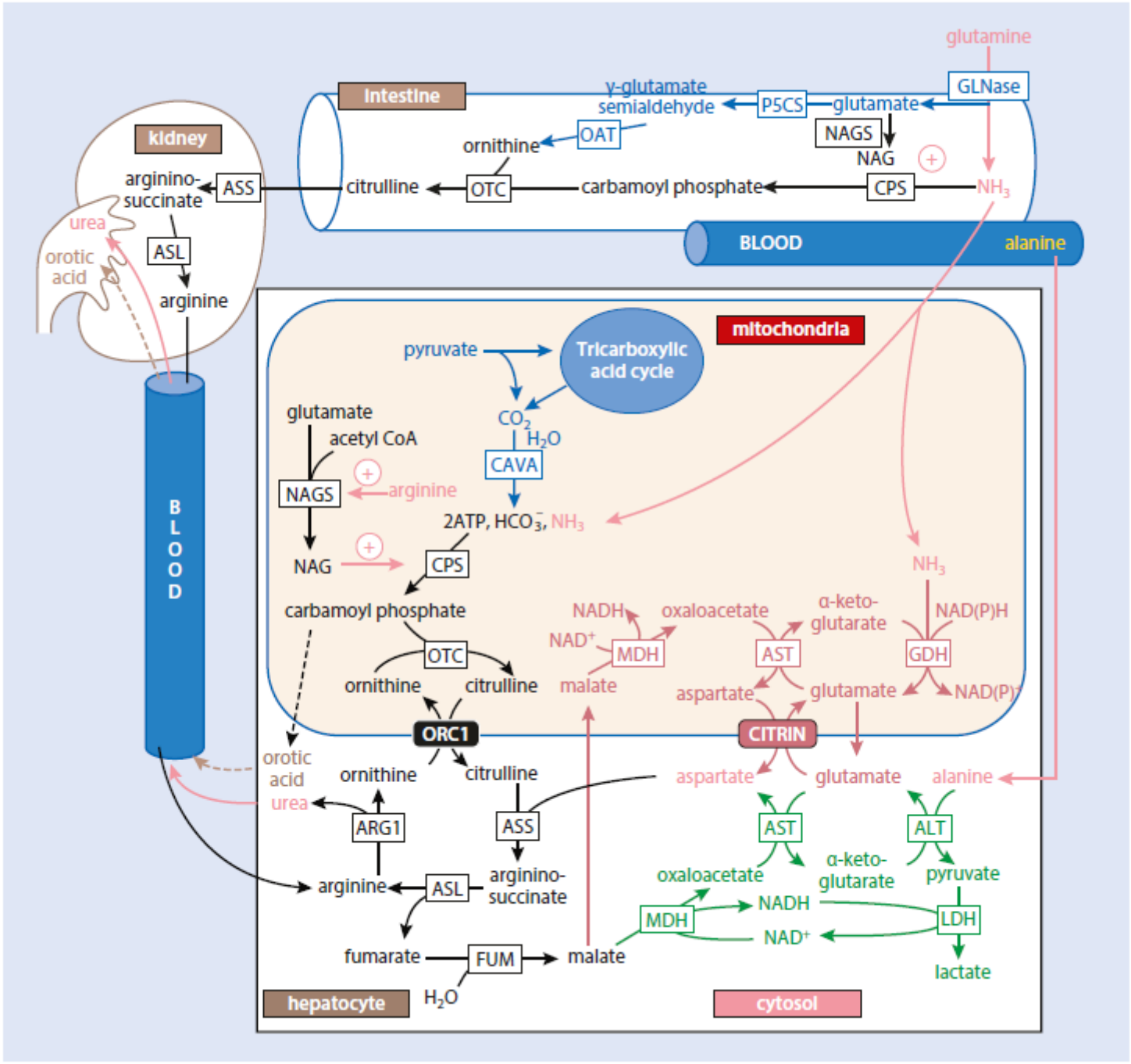
- 42wks of gestation, BW 3.6kg, breastfed till 6months of life
- began eating solid food at 6months, but refuse to eat meat

Since 7 months of age eats cottage cheese dessert



→ apathy, hypotonia, seizures, brain oedema

ALT 4.73, AST 4.1 μmol/l (< 0,6)
Amonnia 396 μmol/l (< 60)


glutamine
GLNase
Intestine
γ-glutamate semialdehyde
P5CS
glutamate
NAGS
NAG
ornithine
OAT
Kidney
arginino-succinate
ASS
citrulline
OTC
carbamoyl phosphate
CPS
NH3
urea
orotic acid
ASL
arginine
BLOOD
alanine
mitochondria
pyruvate
Tricarboxylic acid cycle
CO2
H2O
CAVA
glutamate
acetyl CoA
NAGS
arginine
2ATP, HCO3−, NH3
NAG
CPS
carbamoyl phosphate
NADH
oxaloacetate
α-keto-glutarate
NAD(P)H
NAD+
MDH
AST
GDH
malate
aspartate
glutamate
NAD(P)+
OTC
ornithine
citrulline
ORC1
CITRIN
orotic acid
urea
ornithine
citrulline
aspartate
glutamate
alanine
ARG1
ASS
AST
ALT
arginine
ASL
arginino-succinate
oxaloacetate
α-keto-glutarate
pyruvate
MDH
NADH
NAD+
LDH
fumarate
FUM
malate
lactate
H2O
hepatocyte
cytosol

UCD - derangement

Amonmia < 60 (< 80) μmol/l
> 100 (> 150) – < 250 μmol/l
> 250 μmol/l

Glutamine < 800 μmol/l

Hyperammonia → brain oedema, direct neuro and hepathotoxicity > 250 μmol/l (respiratory alkalosis)

Glutamine ↑neuronal osmotic changes, excitotoxicity

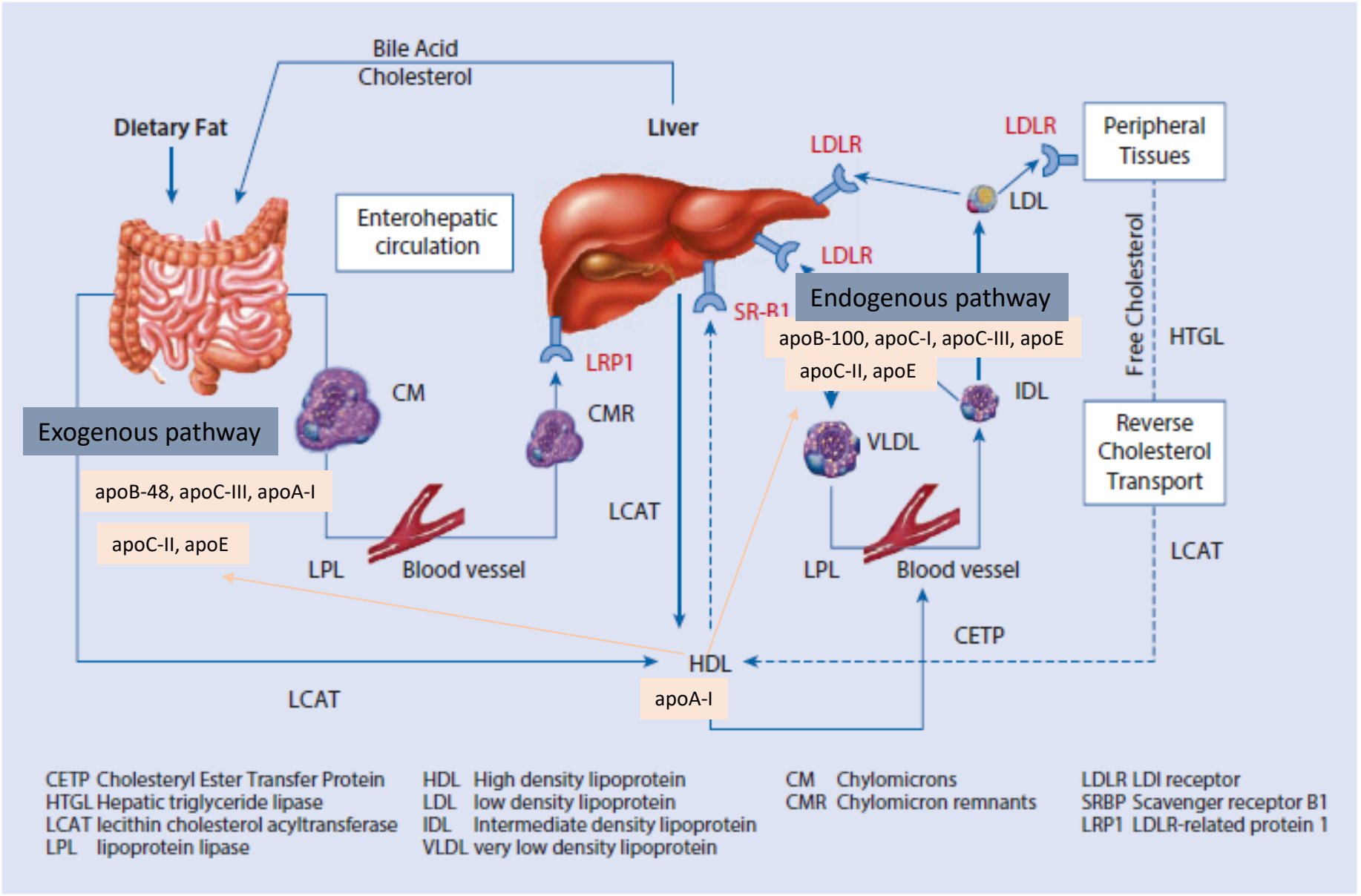
Disorders of lipid metabolism

>210 hum genetic diseases,
in KPDPM dg. >1100 patients

What diseases?

- ✓ Inborn errors of lipoprotein metabolism
- ✓ Fatty acid oxidation disorders
- ✓ Peroxisomal disorders
- ✓ Disorders of cholesterol synthesis
- ✓ Lysosomal storage disorders - sphingolipidoses

Lipoproteins



Saudubray M et al, Inborn Metabolic Diseases, diagnosis and treatment, 7ed, Springer 2022

Dyslipidemias – abnormal lipoprotein and lipid concentration

Primary dyslipidemias – 18 genetic diseases

Dyslipidemias in other primary IMD –

Lysosomal acid lipase def.

Niemann-Pick disease type A, B, C

Sekundary dyslipidemias –

Hypothyreosis

Nephrotic syndrome

Metabolic syndrome

Primary dyslipidemias

↑ Total cholesterol and/or ↑ triglycerides

Receptor for LDL (LDL-R)

AD familial hypercholesterolemia – HeFH (1:250)

AR familial hypercholesterolemia – HoFH (1:300 000)

def. PCSK9 (proprotein convertase subilisin/kexin9) AD inheritance

gain-of-function

Others

Familial ligand-defective apoB-100 (FLDB) – variants in *APOB*

Sitosterolemia – disorders of fytosterols transport

Hypercholesterolemia ↑LDL – risk of developing cardiovascular disease

*aterosklerosis, heart attack, MI, stroke, x*antomas, xantelesmata

Increased thickness of the intima and media of the carotid arteries and calcification of the coronary arteries present in 25% of 11-23 years old HeFH patients.

Disorders of LDL metabolism

AD Familial hyperhypercholesterolemia (LDL receptor)	↑LDL-cholesterol, ↓ HDL cholesterol → xanthomy, xanthelasma, atherosklerosis	Low cholesterol diet (100-300 mg cholesterol/day) Physical activity Pharmacotherapy (Ezetimib, statins,…)
Sitosterolemia (↓ phytosterols excretion)	↑phytosterols, ↑cholesterol, → endothelial disfunction disruption of membrane lipids, hemolysis	Low cholesterol and low phytosterols diet Pharmacotherapy (Ezetimib, statins,…)

Serum lipids at 5yrs and 13yrs if positive family history

Primary dyslipidemias

↓ Total cholesterol and/or triglycerides

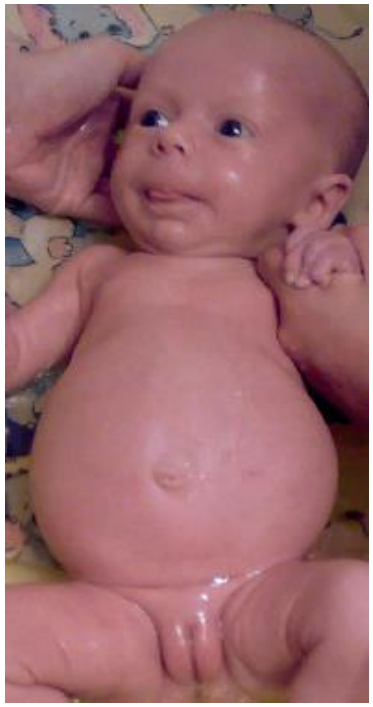
Familial hypobetalipoproteinemia – FHBL
Familial abetalipoproteinemia
Loss of function PCSK9

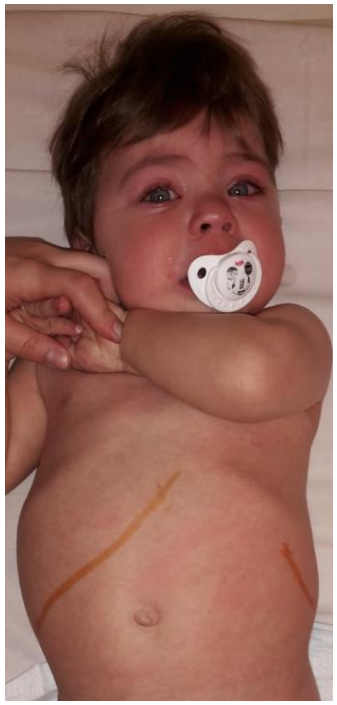
Failure to thrive, fat malabsorption, hepatic steatosis

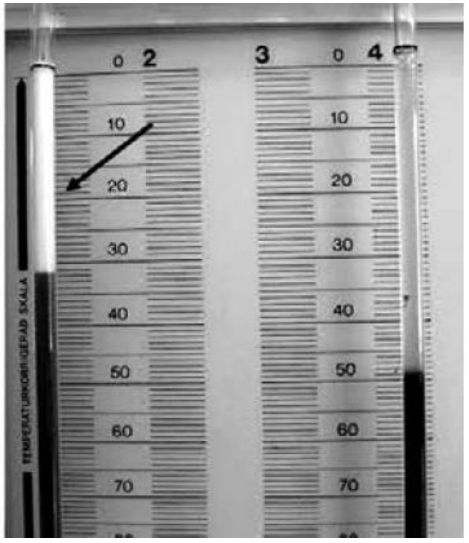
Familial hypoalfalipoproteinemia (Tangier disease)
With variants in *APOA*

Hepatosplenomegaly, peripheral neuropathy, orange enlarged tonsils

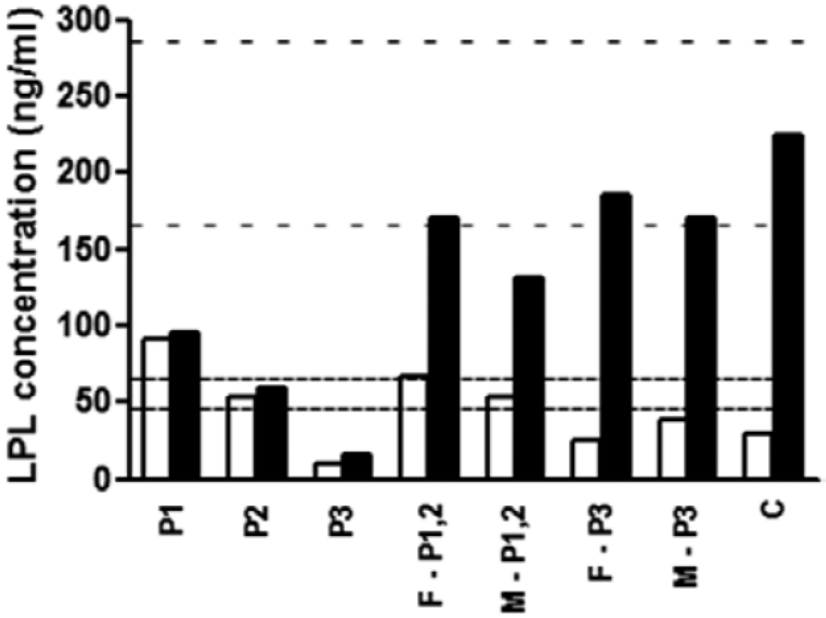
Disorders of Triglycerid metabolism







Hepatosplenomegaly
Steatosis
Lipaemia retinalis
Pancreatitis
↑↑ TG



LPL immunoreactive mass in pre-heparin □ and post-heparin ■ serum in three children with LPL deficiency (P1, P2, P3) compared to their parents.

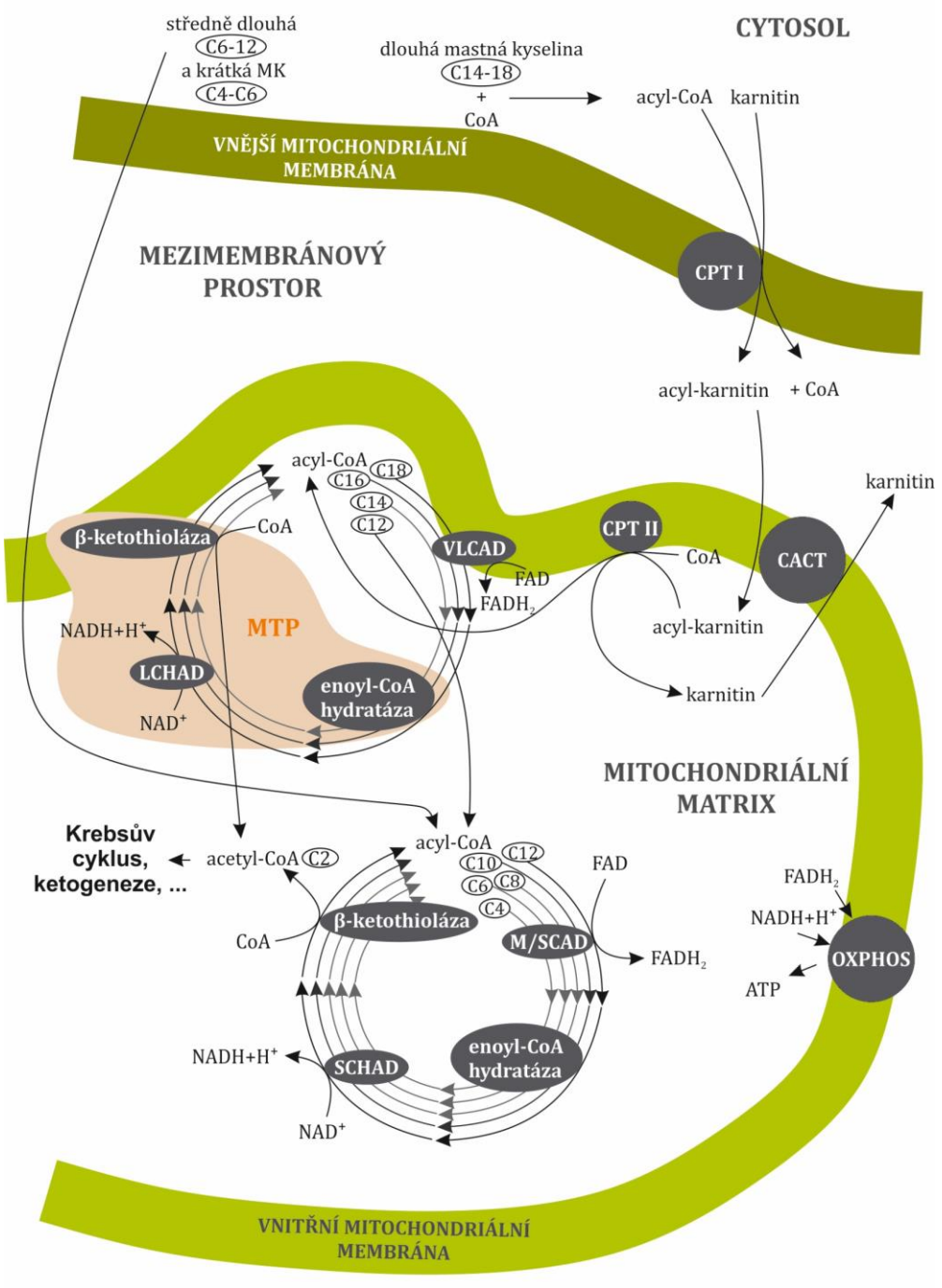
Kolarova H et al., Fol Biol, 2014

Fatty acids metabolism

FAOD – 20 genetic diseases

Fatty acids – 80 % energy during fasting
β-oxidation of FA is absent in neurons and erythrocytes

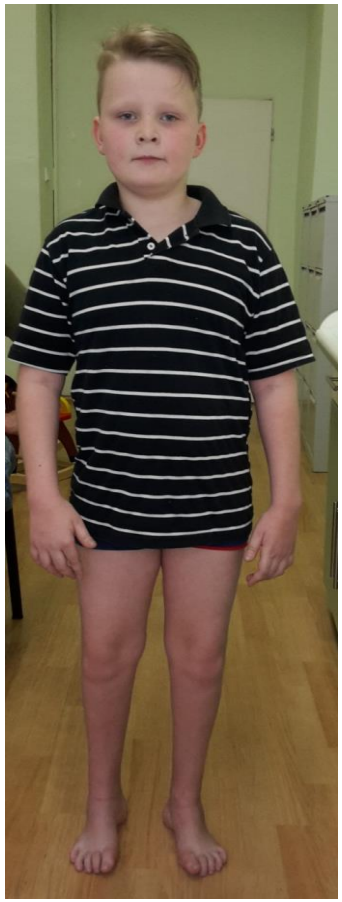
Palmitoyl-CoA → 129 mol ATP
normoglykemia
ketogenesis



Honzík, Zeman ed. (2016) *DMP v kazuistikách*

Disorders of fatty acid oxidation

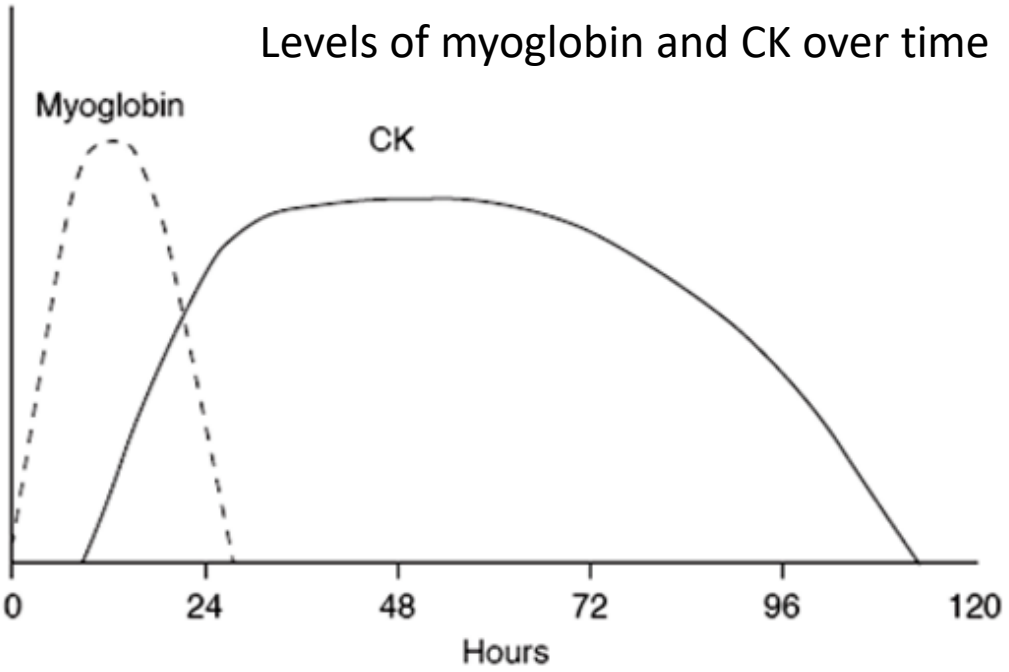
myoglobinuria



Neuropathy – muscle atrophy

- Reye-like illness
- Acute hypoketotic hypoglykaemia
- Rabdomyolysis
- Cardiomyopathy

Levels of myoglobin and CK over time

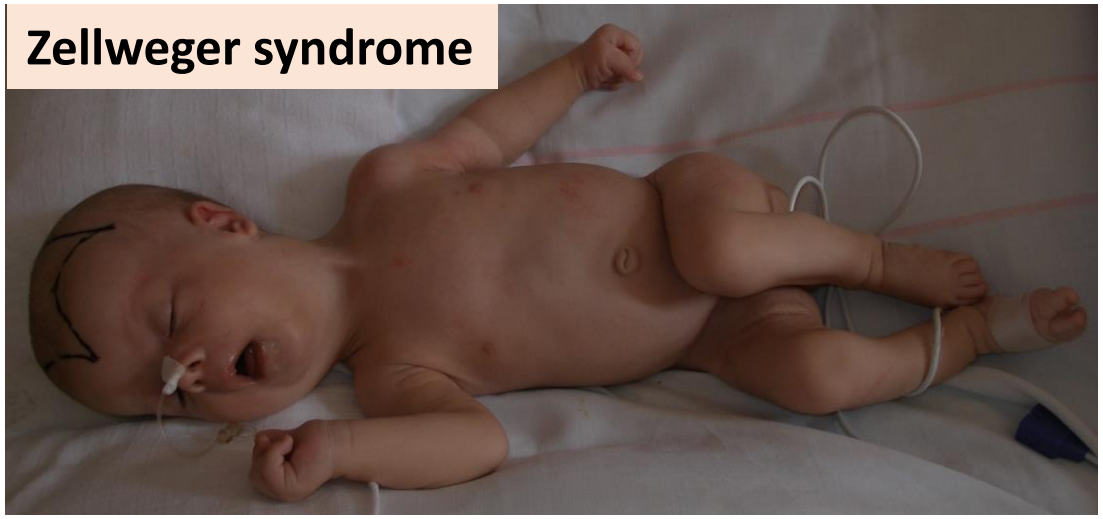


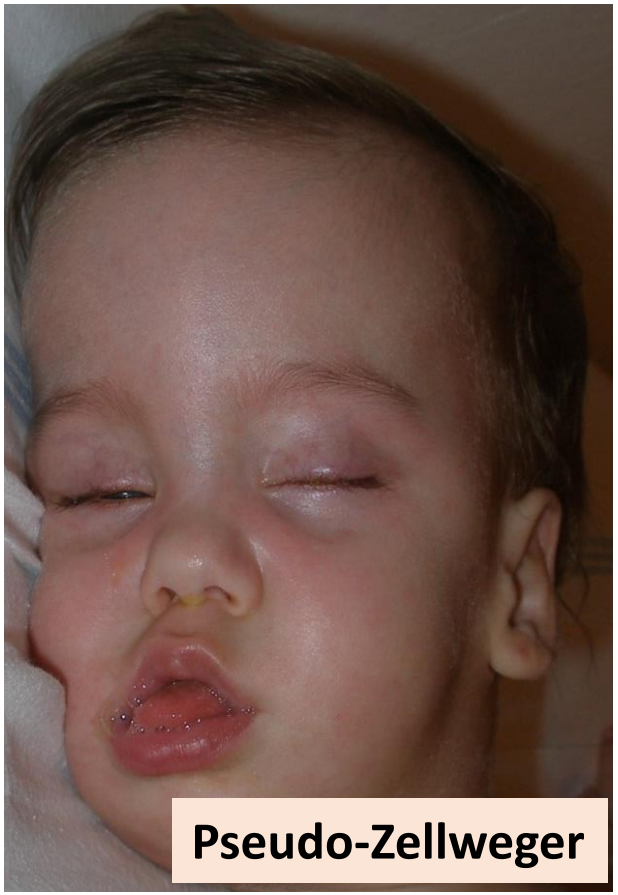
Peroxisoms

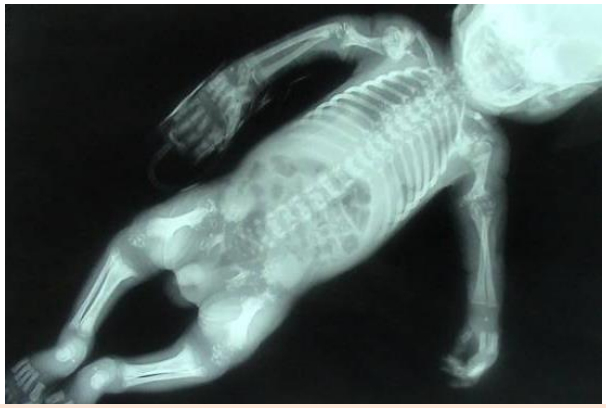
50 enzymes –

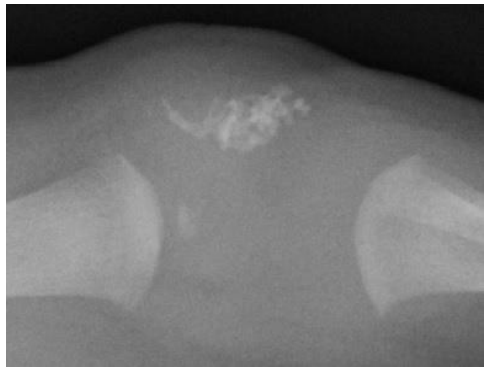
- Oxidation FA >C_{22} *(hexakosanoic C_{26})*
  odd-chain and branched-chain FA
  fytanic $\rightarrow$ *pristanic acid*
- Synthesis of ether phospholipids
  (plasmalogens, PAF)
- cholesterol and isoprenoid biosynthesis
- Synthesis of docosadexaenoic acid (C_{22}:6ω3)
- Glykolate detoxification
- Pipekolic acid oxidation
- Hydrogen peroxide detoxification

Peroxisomal disorders





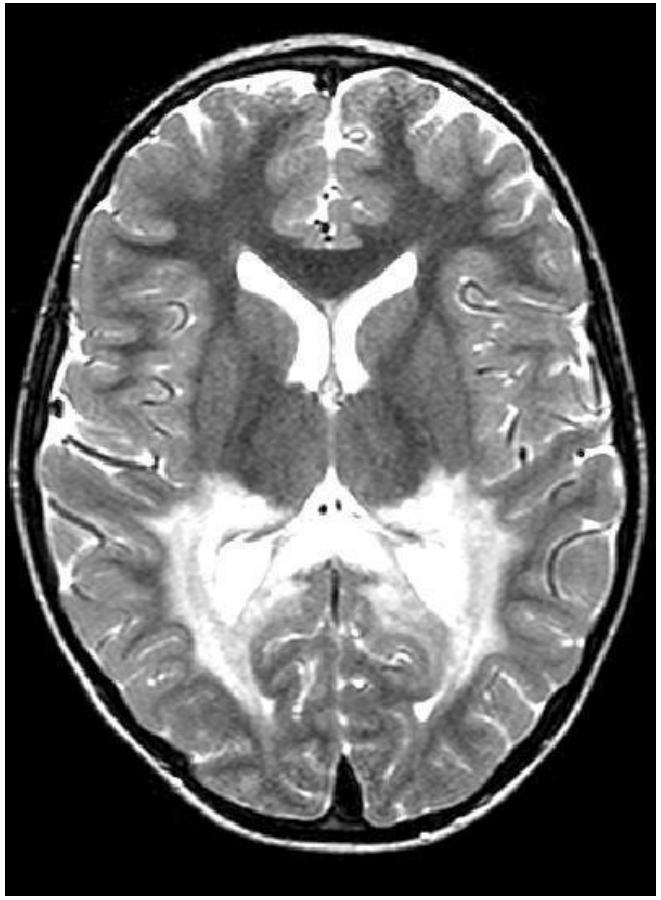




Rhizomelic chondrodysplasia punctata

Hypotonia, psychomotor delay, a wide fontanelle, high forhead, small upturned nose, midface hypoplasia, stippled calcification, rhizomelia

X-linked adrenoleukodystrophy

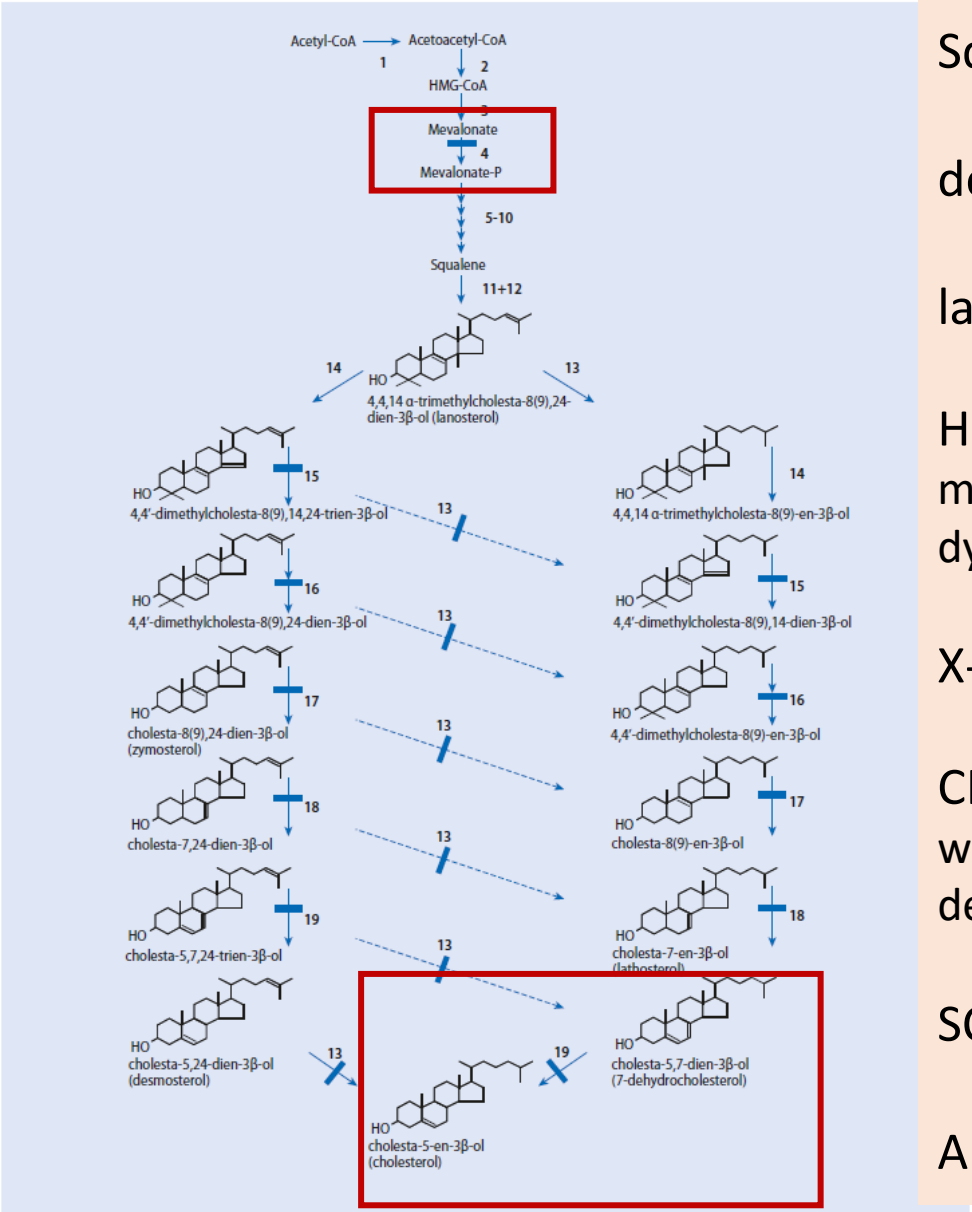


9-months´ time

- 7yrs – weakness of lower extremities
- School failure - attantion deficit
- Ataxia
- Hearing impairment
- Hyperproteinorhachia 2g/l
- Leukodystrophy

CAVE - adrenal insufficiency

Disorders of cholesterol biosynthesis



Mevalonate kinase def.

Squalensynthase def.

desmosterolosis

lathosterolosis

HEM dysplasia (hydrops-ectopic calcification-moth-eaten skeletal dysplasia or Greenberg dysplasia)

X-linked chrondrodysplasia punctata

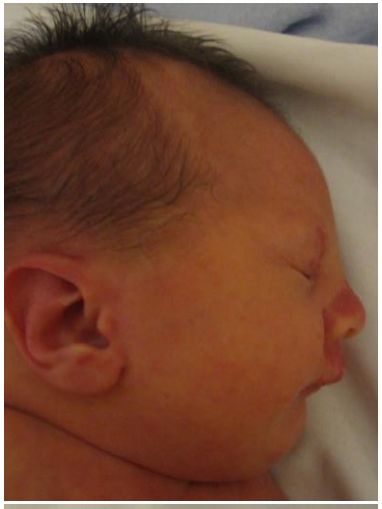
CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects)

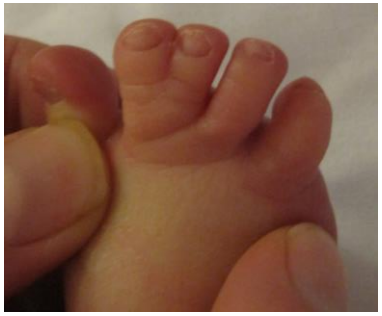
SC4MOL def.

Antley-Bixleyův syndrome

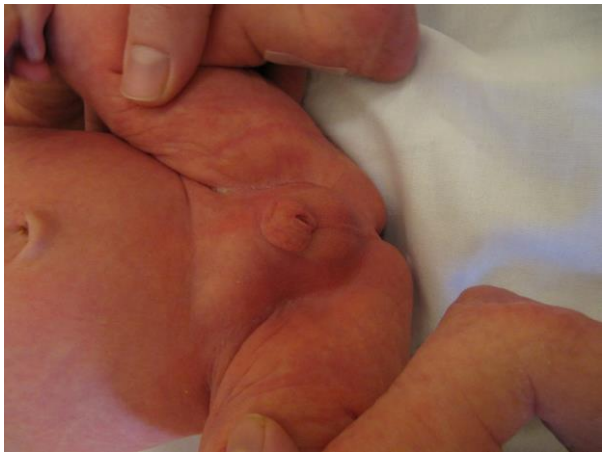
Saudubray M et al, Inborn Metabolic Diseases, diagnosis and treatment, 7ed, Springer 2022

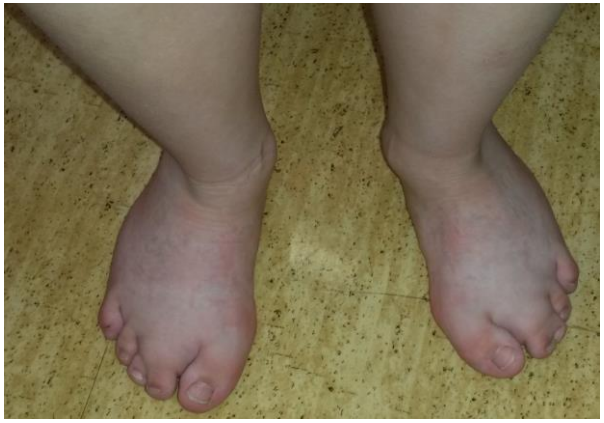
Smith-Lemli-Opitz syndrome



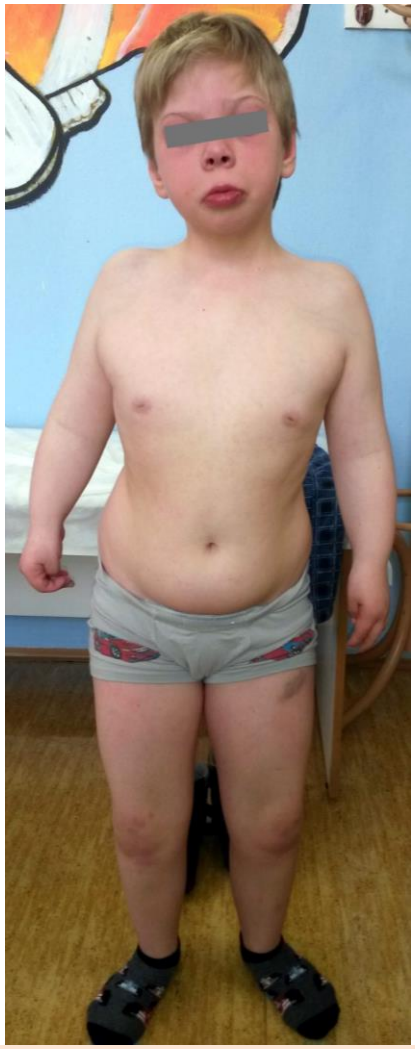


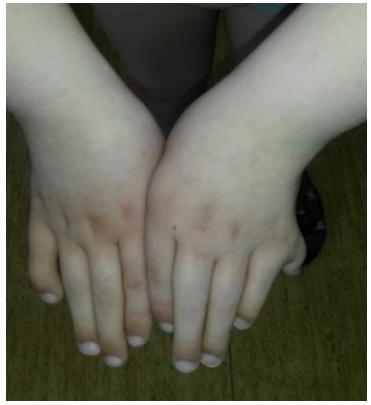
newborn

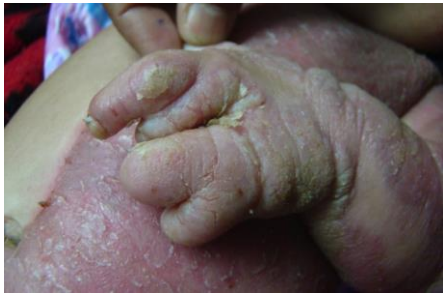




9yrs old boy

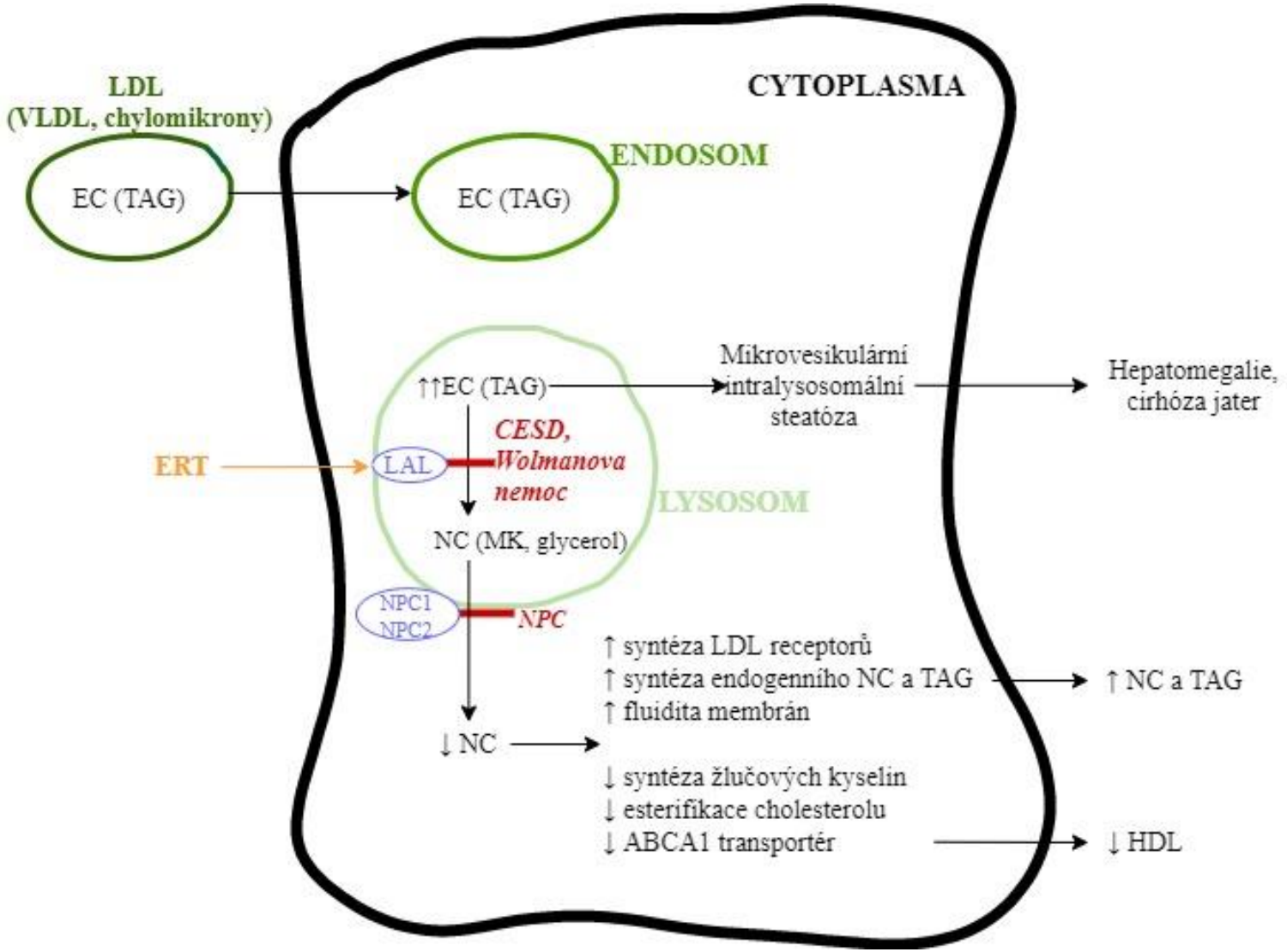




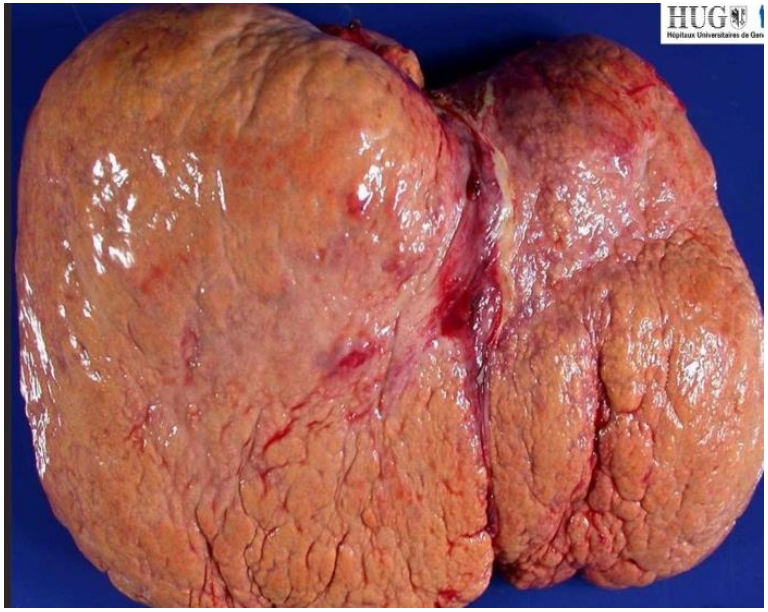


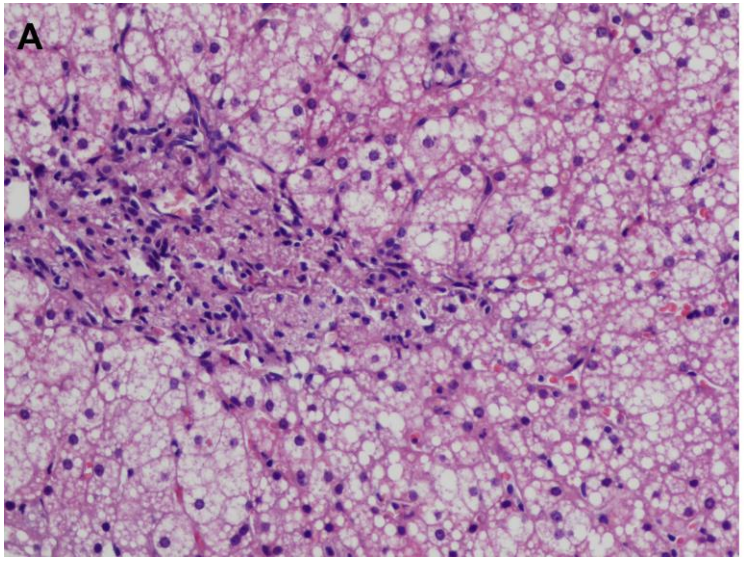
Desmosterolosis, lathosterolosis,
CHILD syndrom, Conradi-Hünermannův syndrom

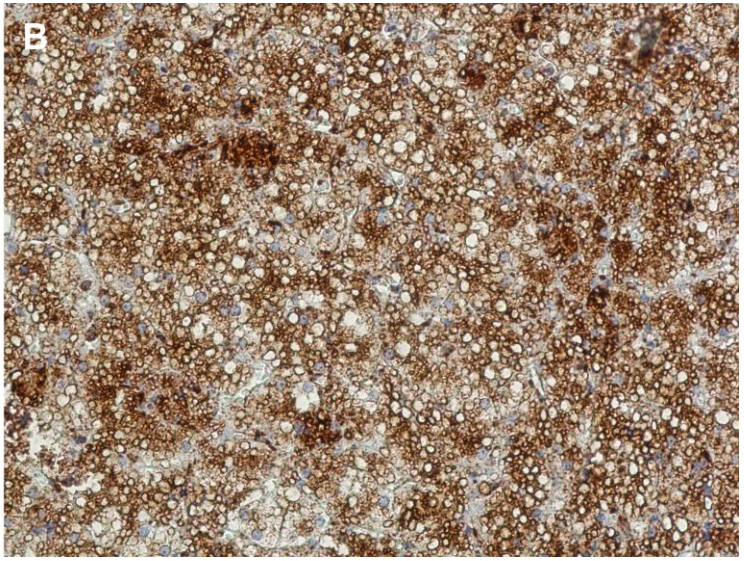
Lysosomal acid lipase deficiency



Lysosomal acid lipase deficiency

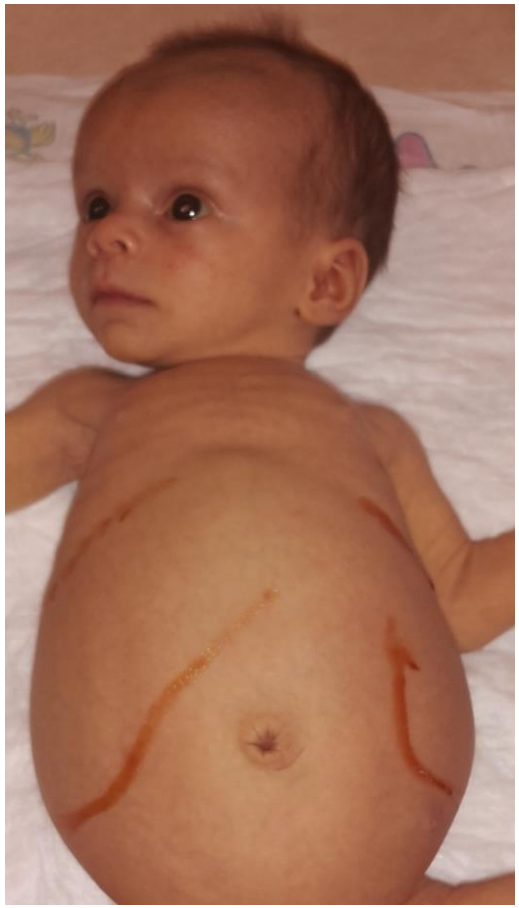


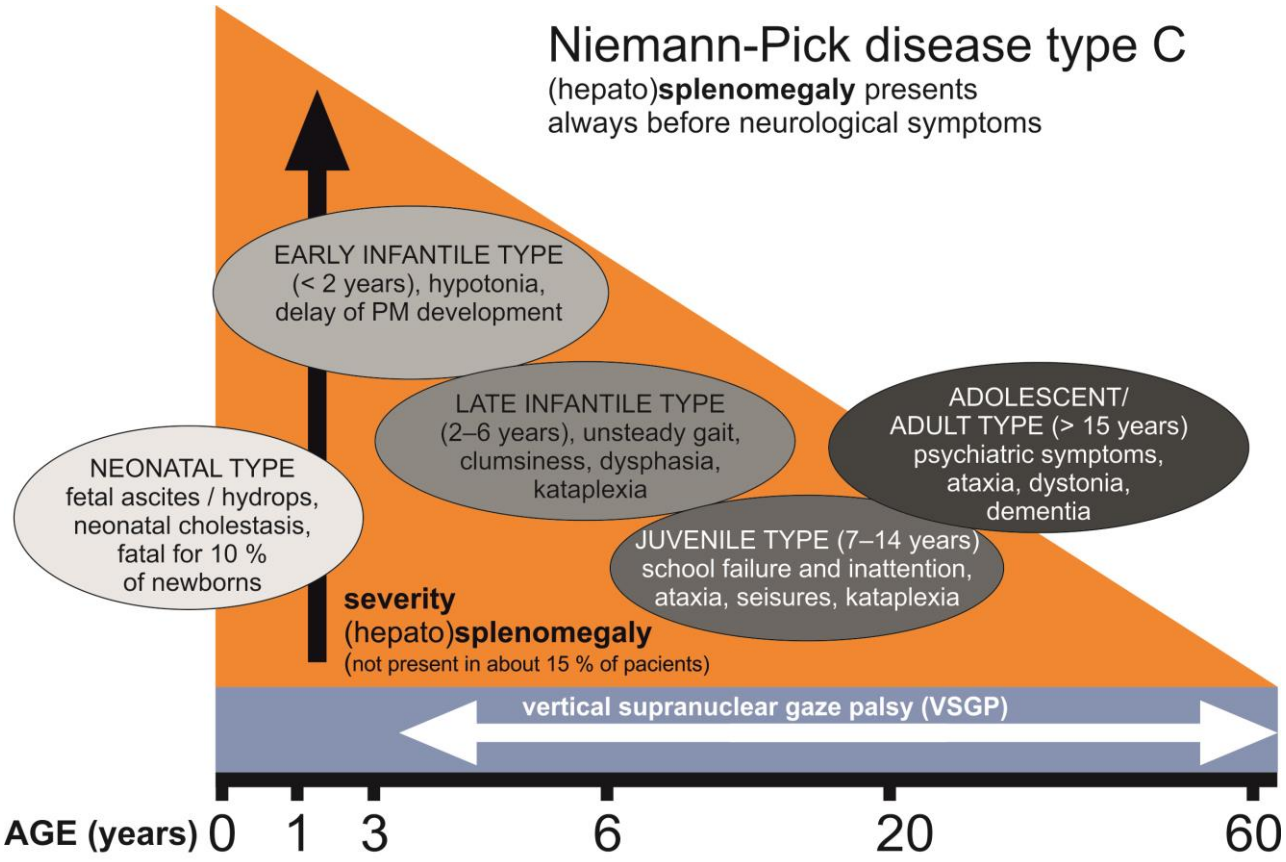




Niemann-Pick type C

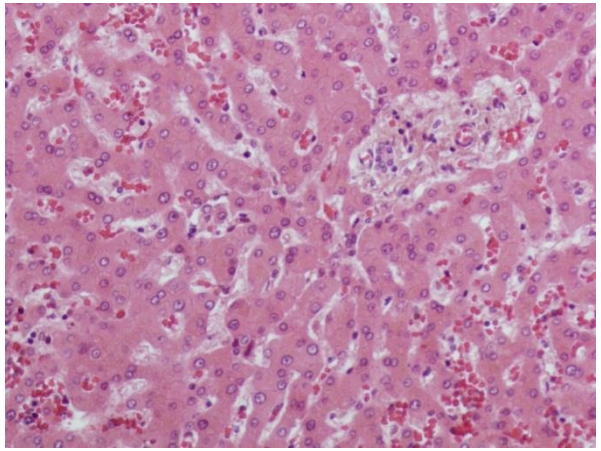
Hepatosplenomegalia
Dyslipidemia
Cholestatis, ↑ SPC 509
↑ chitotriosidase

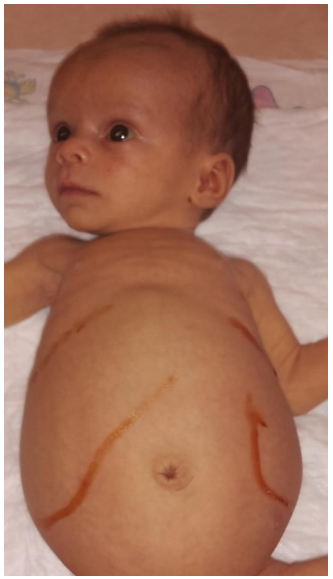


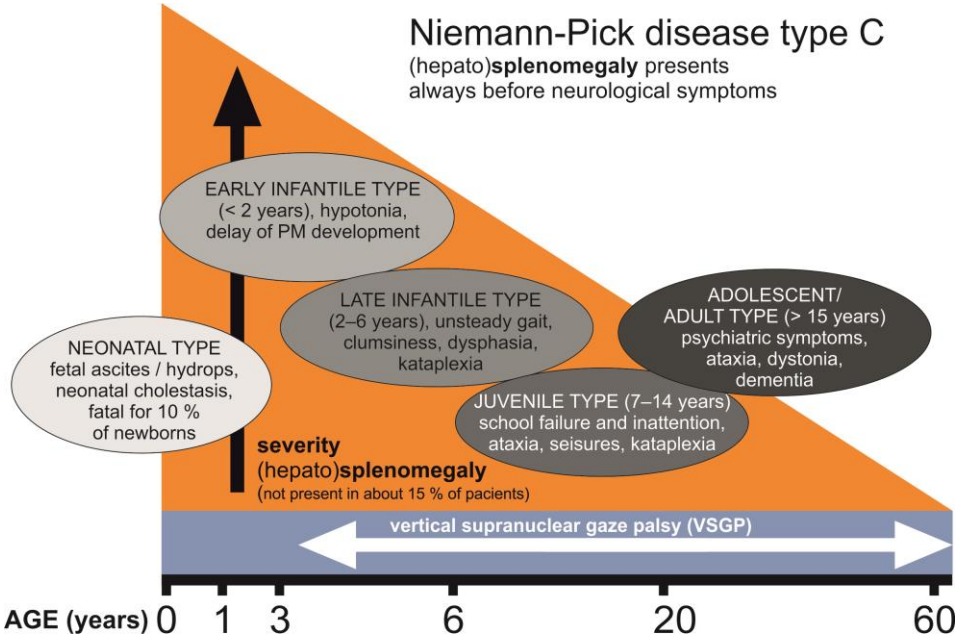


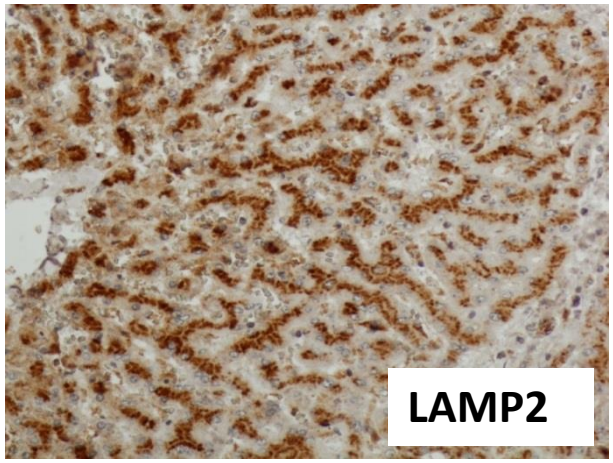
Niemann-Pick disease type C

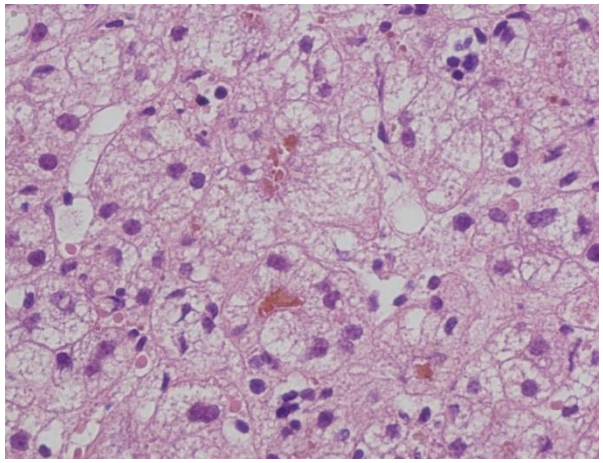
Hepatosplenomegaly
Dyslipidemia
Cholestatis
↑ chitotriosidase

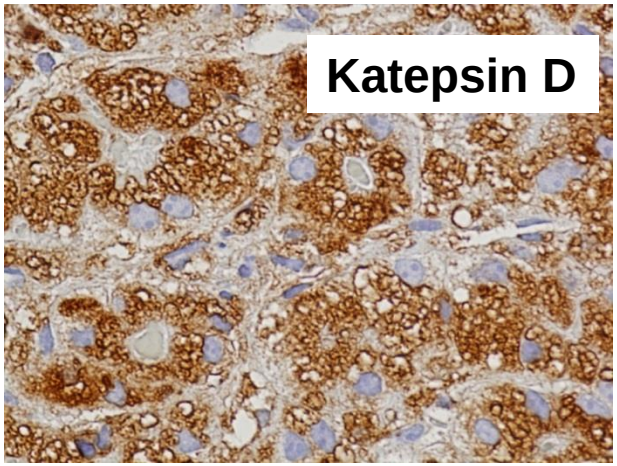


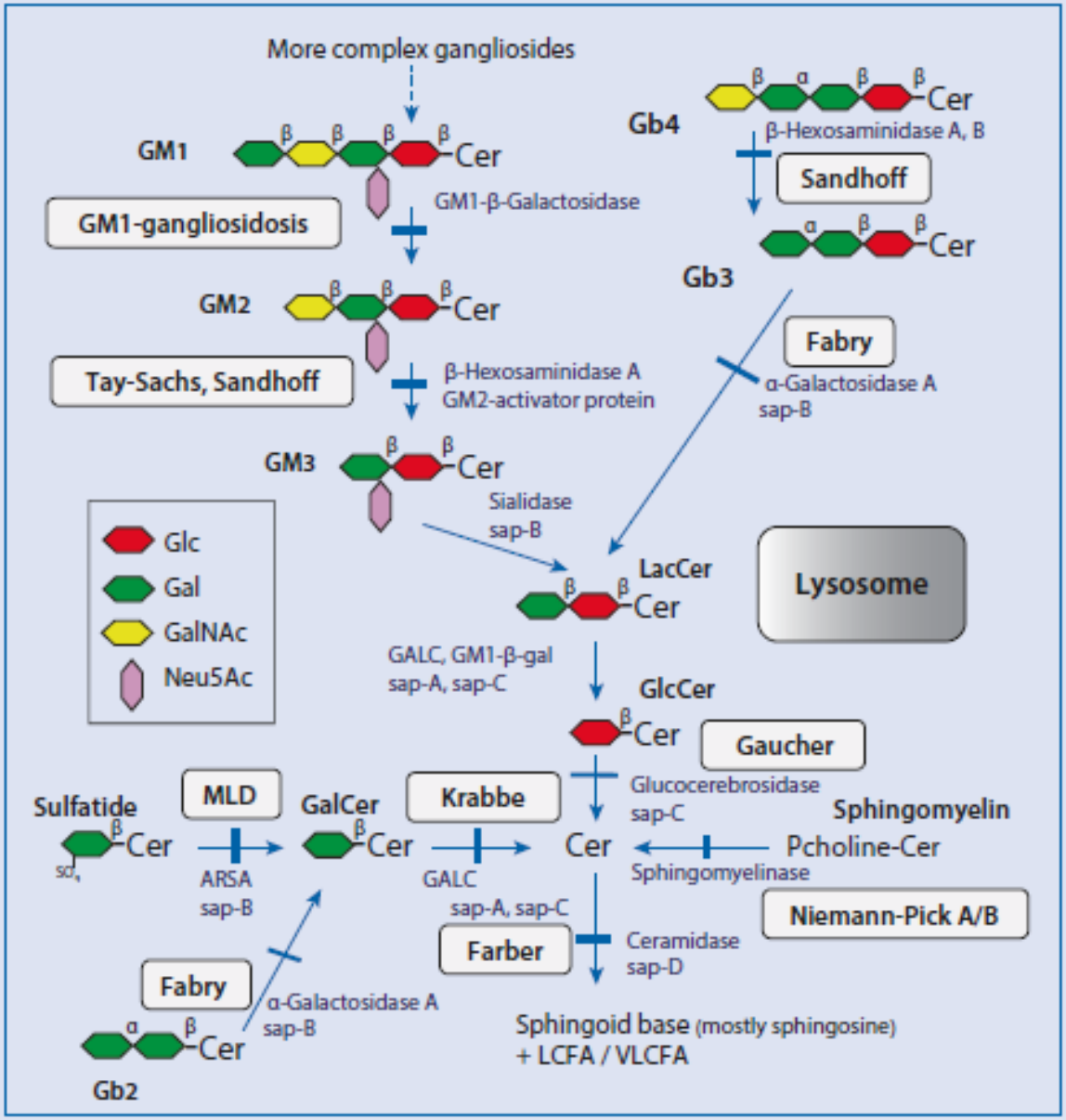






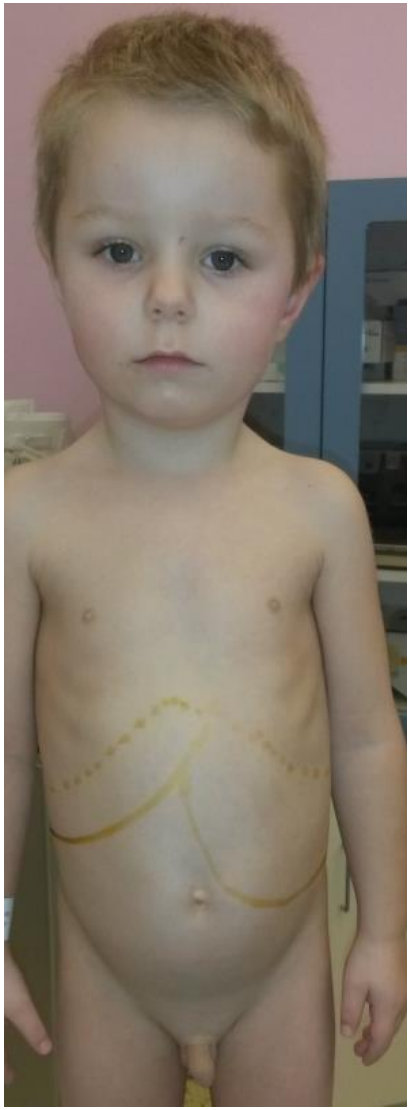


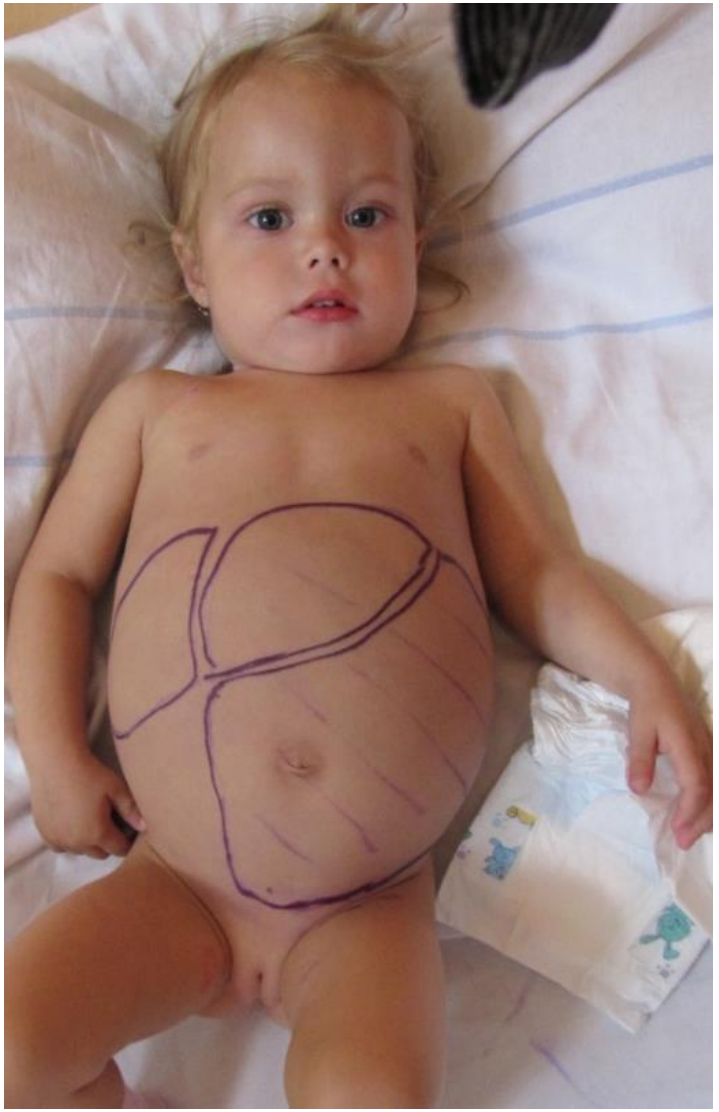



More complex gangliosides
GM1
Cer
GM1-gangliosidosis
GM1-β-Galactosidase
GM2
Cer
Tay-Sachs, Sandhoff
β-Hexosaminidase A
GM2-activator protein
GM3
Cer
Sialidase
sap-B
Gb4
Cer
β-Hexosaminidase A, B
Sandhoff
Cer
Gb3
Fabry
α-Galactosidase A
sap-B
Glc
Gal
GalNAc
Neu5Ac
LacCer
Cer
Lysosome
GALC, GM1-β-gal
sap-A, sap-C
GlcCer
Cer
Gaucher
Glucocerebrosidase
sap-C
Sulfatide
Cer
MLD
ARSA
sap-B
GalCer
Cer
Krabbe
GALC
sap-A, sap-C
Cer
Sphingomyelin
Pcholine-Cer
Sphingomyelinase
Niemann-Pick A/B
Farber
Ceramidase
sap-D
Fabry
α-Galactosidase A
sap-B
Cer
Gb2
Sphingoid base (mostly sphingosine)
+ LCFA / VLCFA

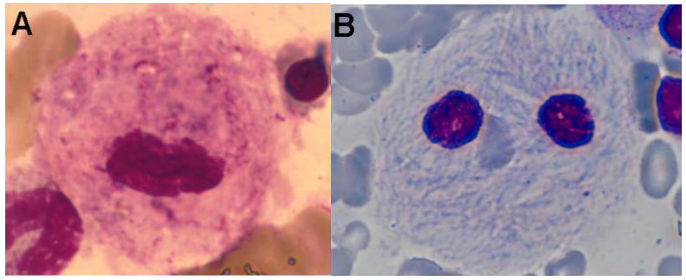
Gaucher disease

Hepatosplenomegaly
Steatosis
Thrombocytopenia
Bone crises
↑↑ chitotriosidase
Gaucher cells
in bone marrow

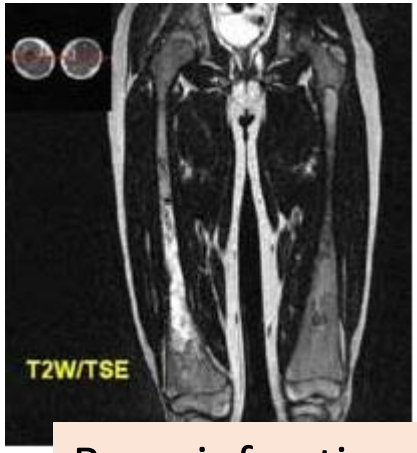




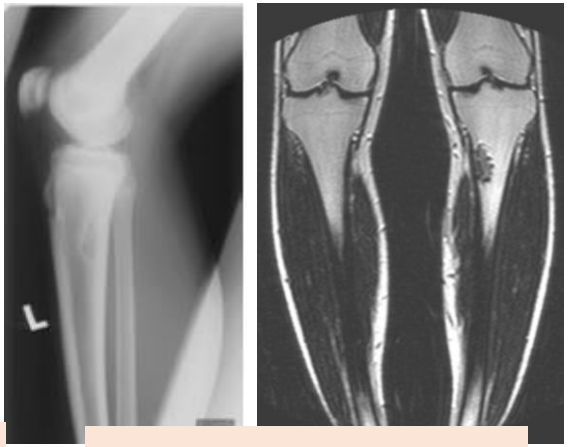
Gaucher disease



Bone marrow– Gaucher cells

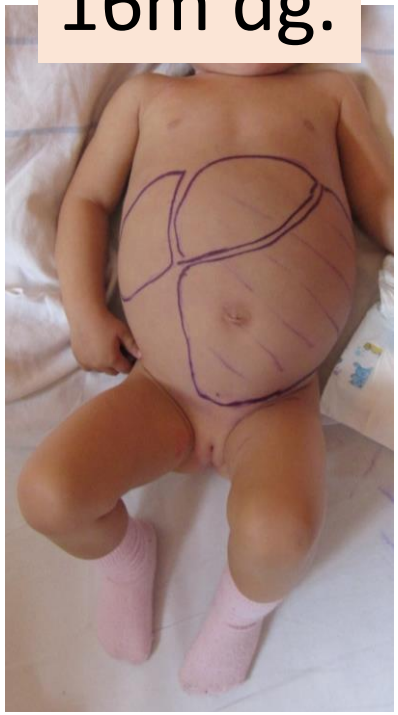


Bone infarction

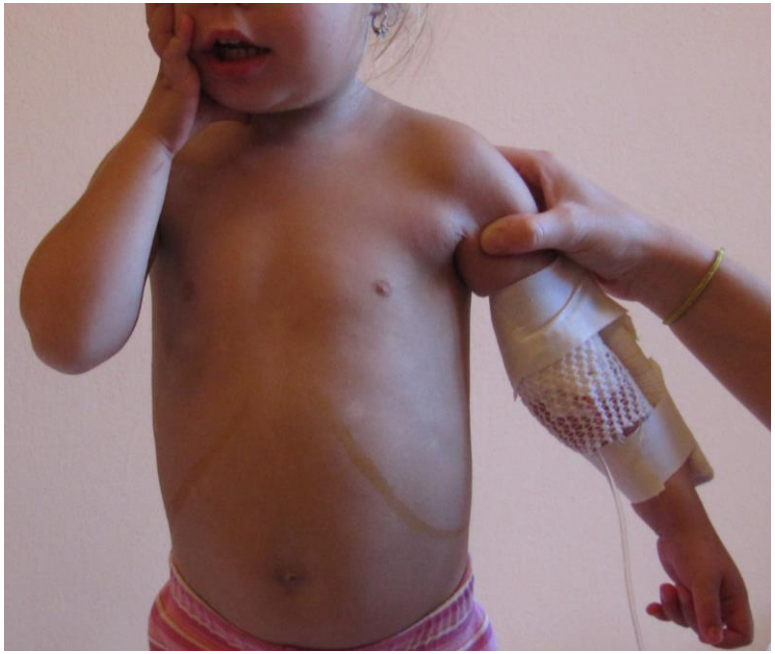


Osteolytic lessions

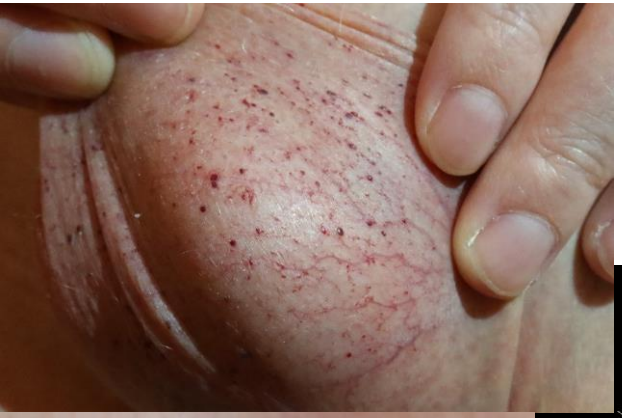
16m dg.

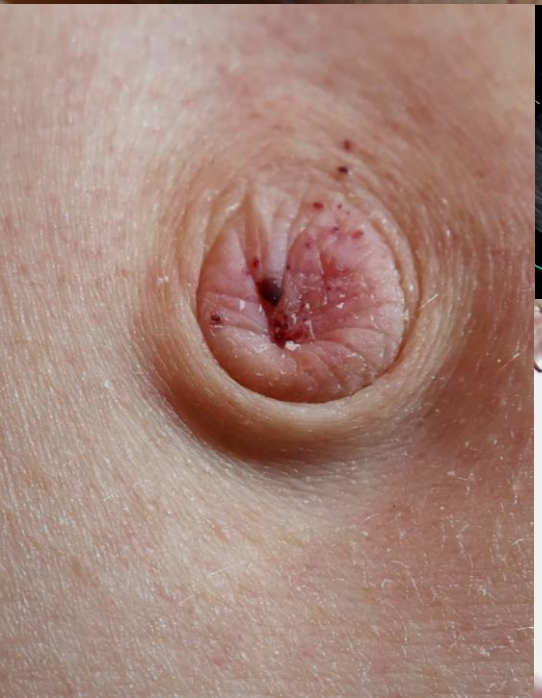


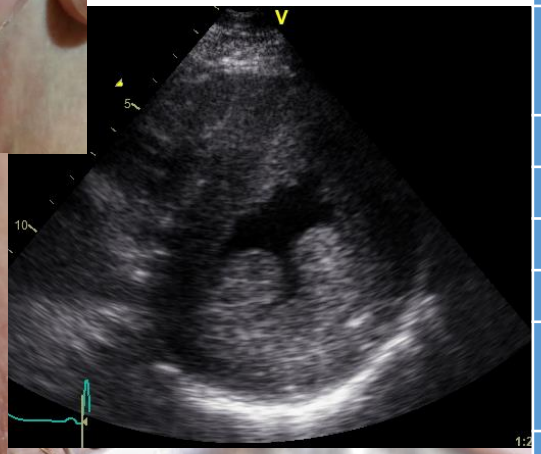
15m na ERT→

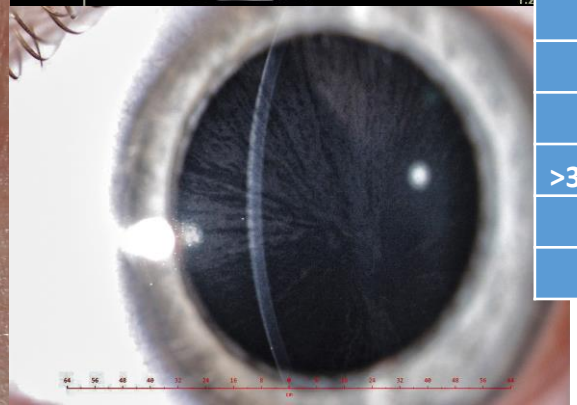


Fabry disease









the most common age of symptom onset	symptom
childhood and adolescence	neuropatic pain
	hypohidrosis
	acroparestetic crisis
	cornea verticillata, convoluted vessels of the retina
	hearing impairment
	angioceratoma
	microalbuminuria
	GIT complains
The second decade of life	cardiomyopathy
	TIA, stroke
	proteinuria
	↓ GFR
>30yrs	Progress of organ disfunction
	Organ failure
	Premature death

Disorders of carbohydrate metabolism

>250 hum genetic diseases,
in KPDPM dg. >360 patients

What diseases?

- ✓ Classic galaktosemia
- ✓ Hereditary fructose intolerance
- ✓ Hepatic glycogenoses
- ✓ Pompe disease
- ✓ Mucopolysaccharidosis

Classic galactosemia

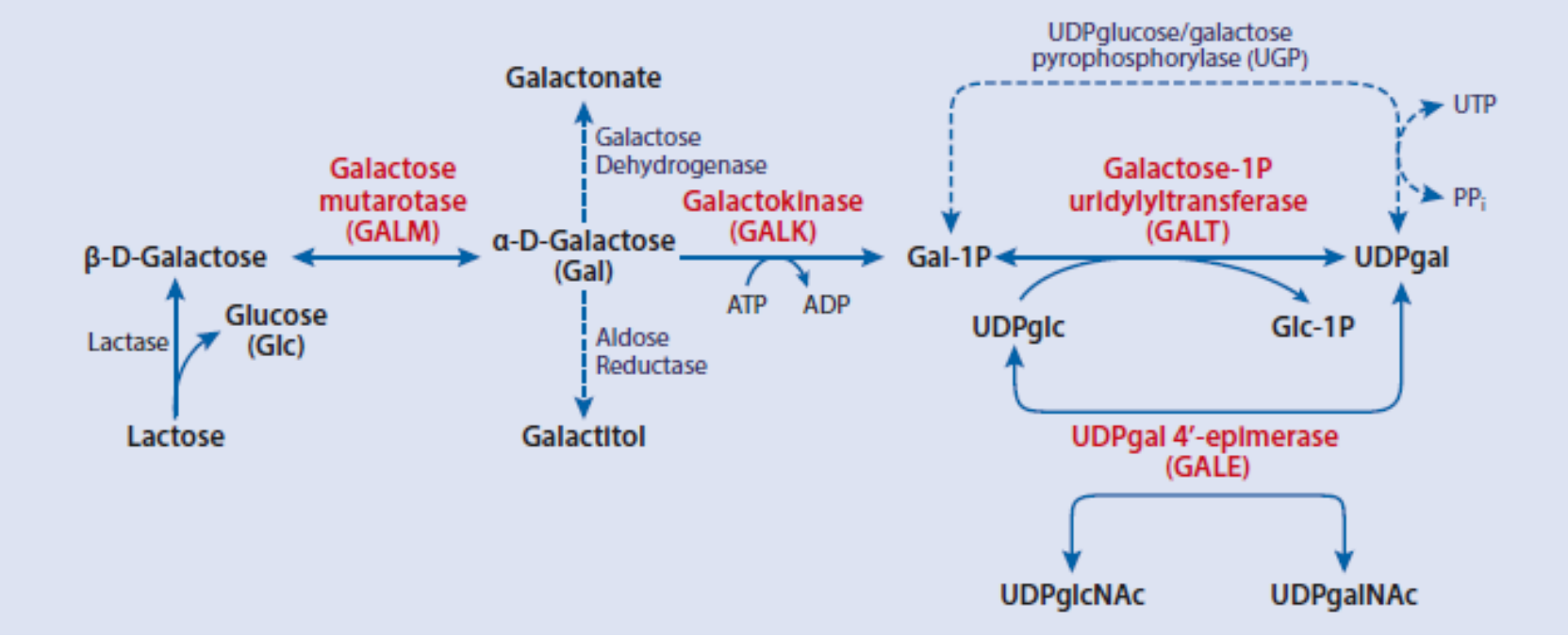
- Vomiting
- Weight loss
- Jaundice
- Hepatomegaly
- Cataract

ALT 3.4 µkat/l (N<0.6)
AST 4.7 µkat/l (N <0.63)
Bilirubin 407 µmol/l (N <100)
Conj. bilirubin 97 µmol/l (N <20%)
Glycemia 0.6 mmol/l (N 3.3-5.4)
INR 6.5 (N 0.8-1.2)
APTT >180s (N 26-40)
Ammonia 101 µmol/l (N <80)

Acute liver failure with mixed hyperbilirubinemia

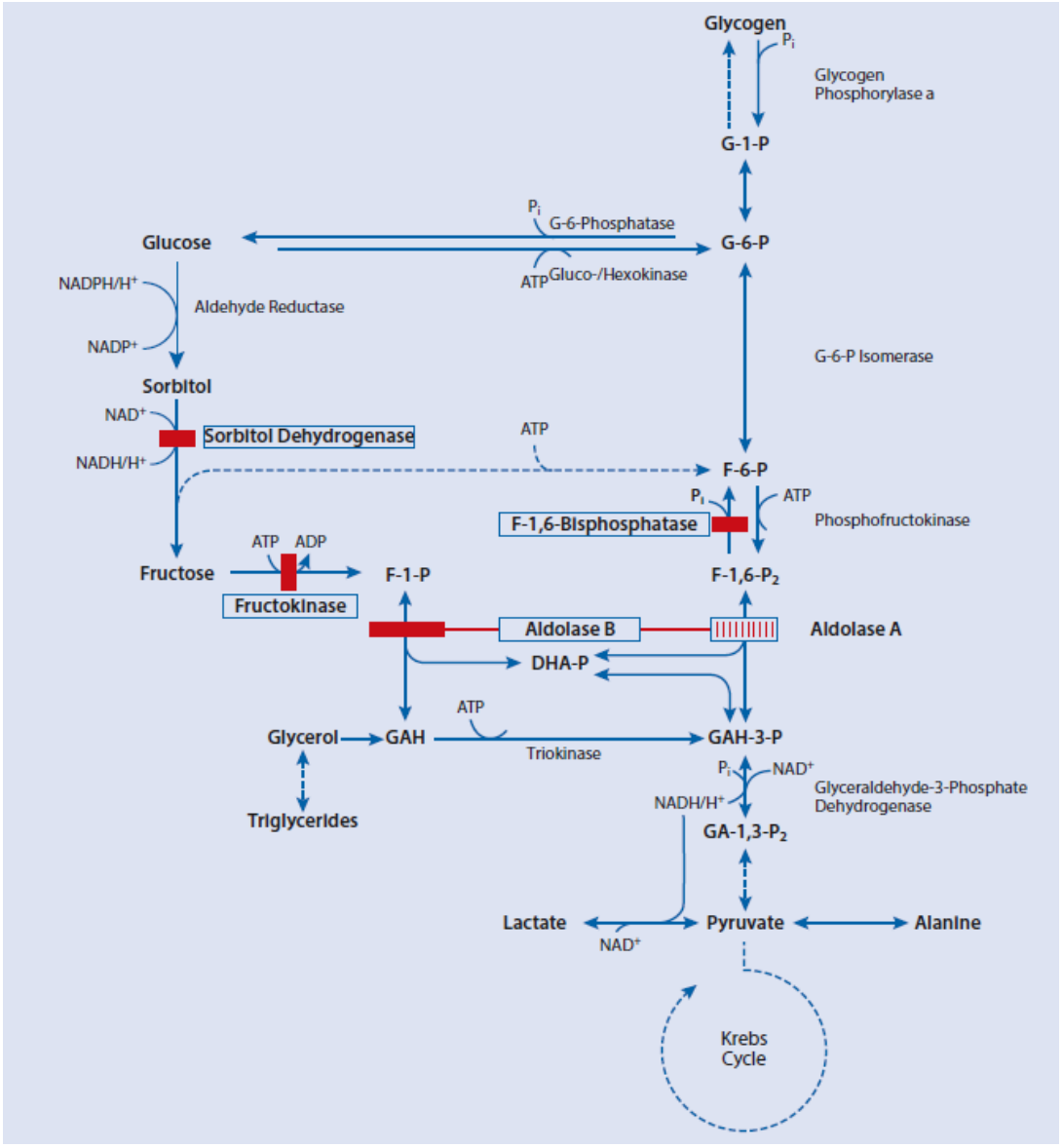
Classic galactosemia

» ↑ Galactitol: toxic – liver, kidney, lens, brain
» ↑ Gal-1-P: ↓ Glu-6-P→Glc; ↓ Glykogenolysis
» ↓ inorganic phosphate
» ↓ UDP Gal: ↓ glycosylation of protein



Saudubray M et al, Inborn Metabolic Diseases, diagnosis and treatment, 7ed, Springer 2022

HFI



Fruits and vegetables	Fructose content(g) in 100 g food
Honey	39
Raisins	33
Dried dates	31
Dried apples	29
Dried figs	25
Jams	20
Grapes	13.6
Soft drinks	12.5
Dried plums	11
Pears	7
Apples	6
Cherries	6

- Hepatomegaly
- FTT
- Hepatopathy/liver failure
- Hypoglycemia
- Fanconi syndrome

Glykogen

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 22 1957

CLAUDE BERNARD AND THE DISCOVERY OF GLYCOGEN

A CENTURY OF RETROSPECT*

BY

F. G. YOUNG, D.Sc., Ph.D., F.R.S.

Department of Biochemistry, University of Cambridge

sugar-forming substance –
„la matiere glycogene" 1857

Carl and Gerty Cori, Science History Institute, Bernard Becker Medical Library, Washington University School of Medicine.

XX.

Hepato-Nephromegalia glykogenica.

(Glykogenspeicherkrankheit der Leber und Nieren.)

Von

E. von Gierke.

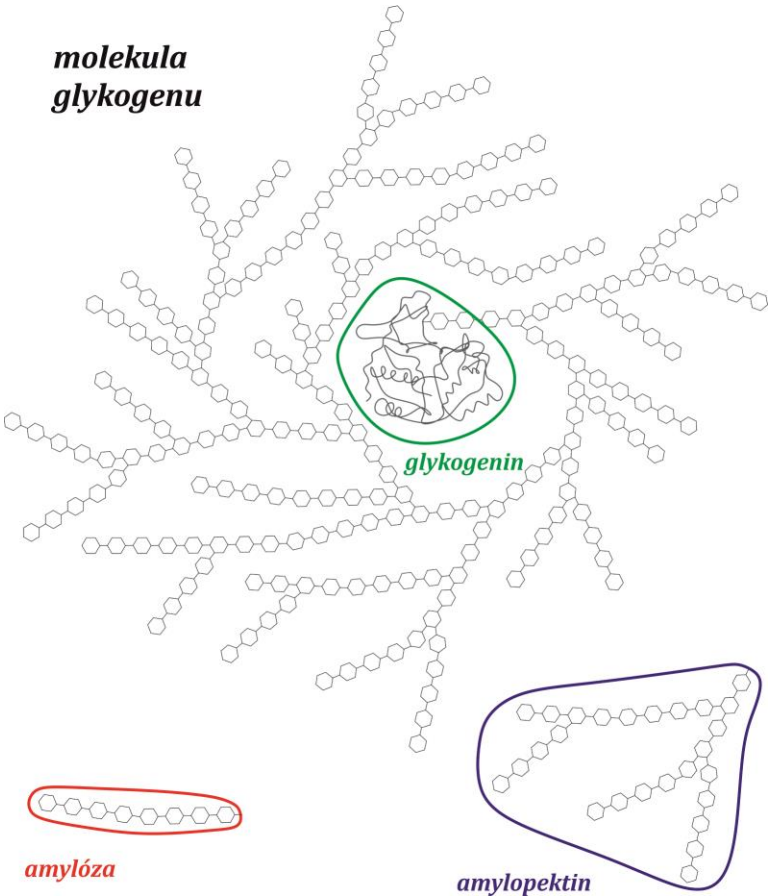
Aus der Prosektur des Städtischen Krankenhauses Karlsruhe i. B.
(Vorstand: Prof. Dr. v. GIERKE.)

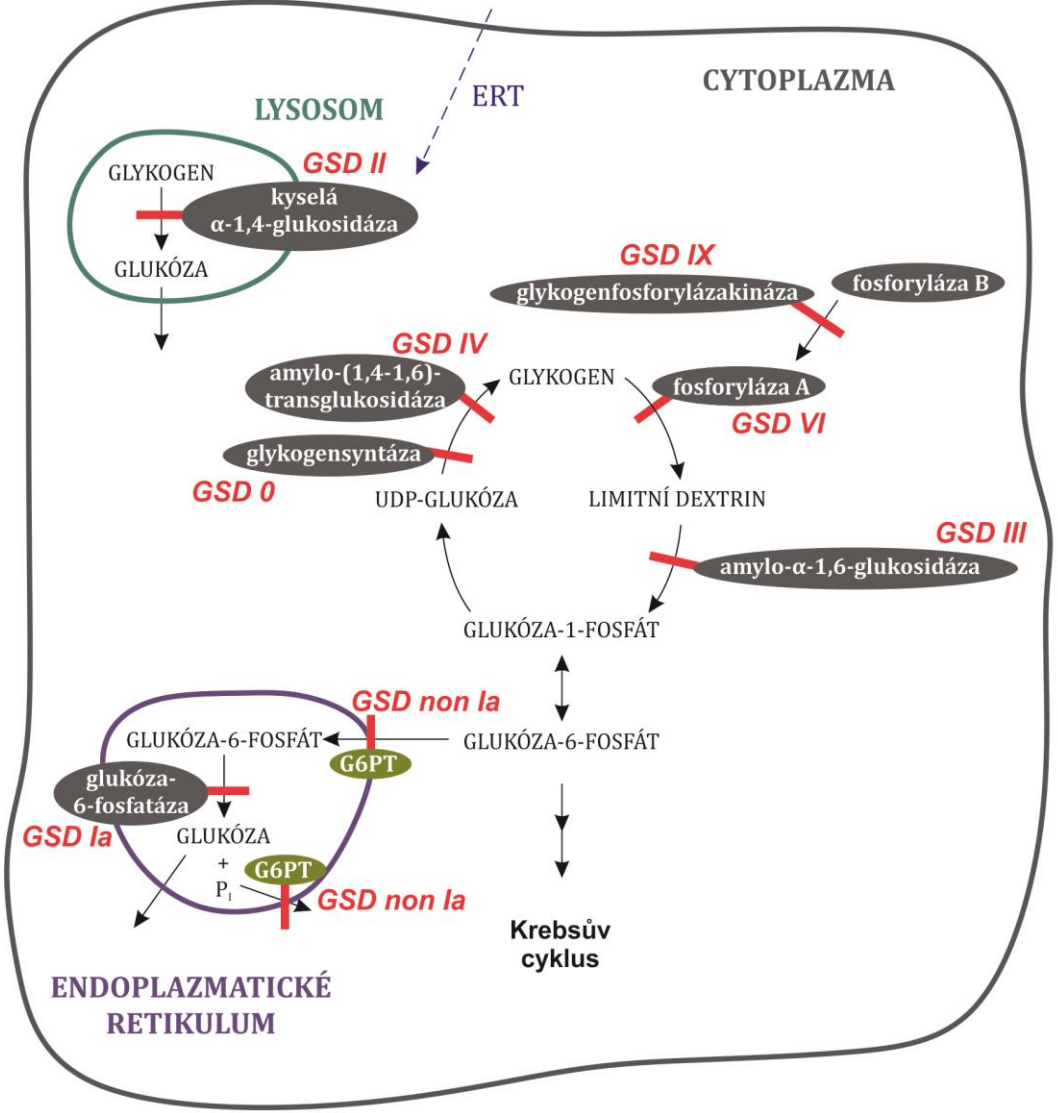
Mit 1 Abbildung im Text und Tafel XVI.

(Eingegangen am 21. März 1929.)

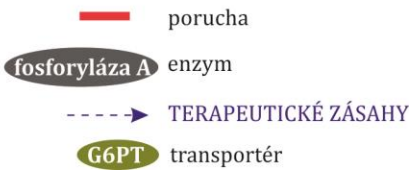
Glykogen – 30000–60000 glc residue

glykogen in liver 8–10 % of weight (150g)
glykogen in muscles 2 % of weight (1000g)

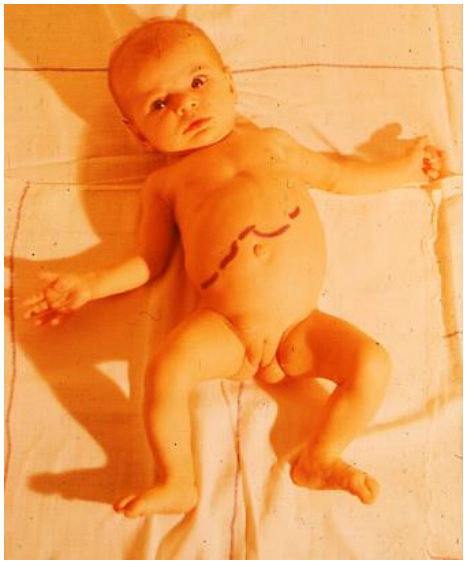


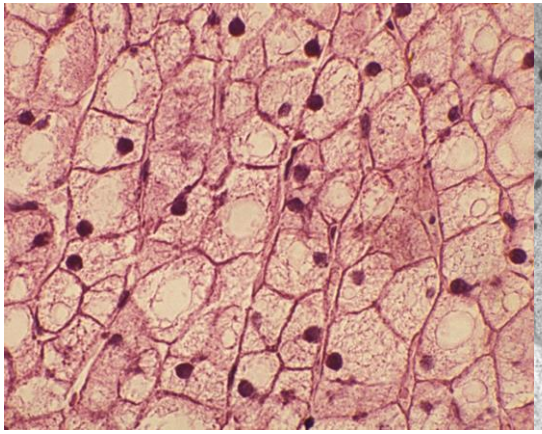


Honzík, Zeman ed. (2016) *DMP v kazuistikách*

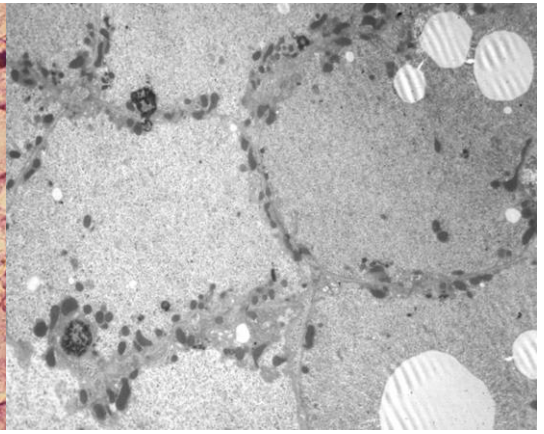


Glykogenosis type Ia



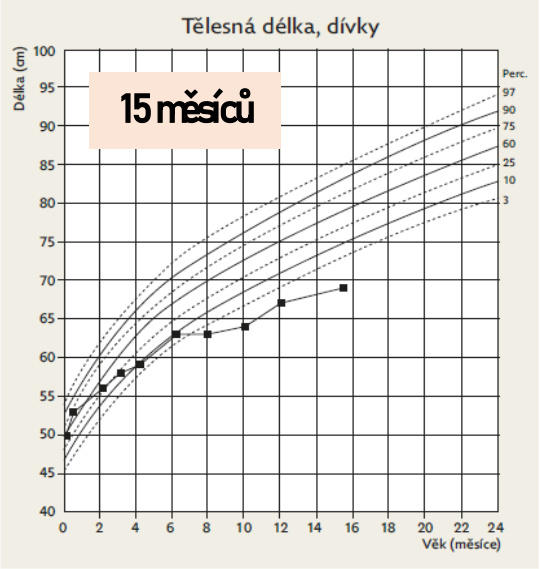


Světelná mikroskopie (H&E, 400x)



ELM (3000x)

- hepatomegalia
- hepatopathy
- growth failure
- dyslipidemia
- hypoglycemia
- hyperuricemia
- lactic acidosis



Late dg at the age of 15 months

Boris Senior, M.D.,* and Liliane Loridan, M.D.

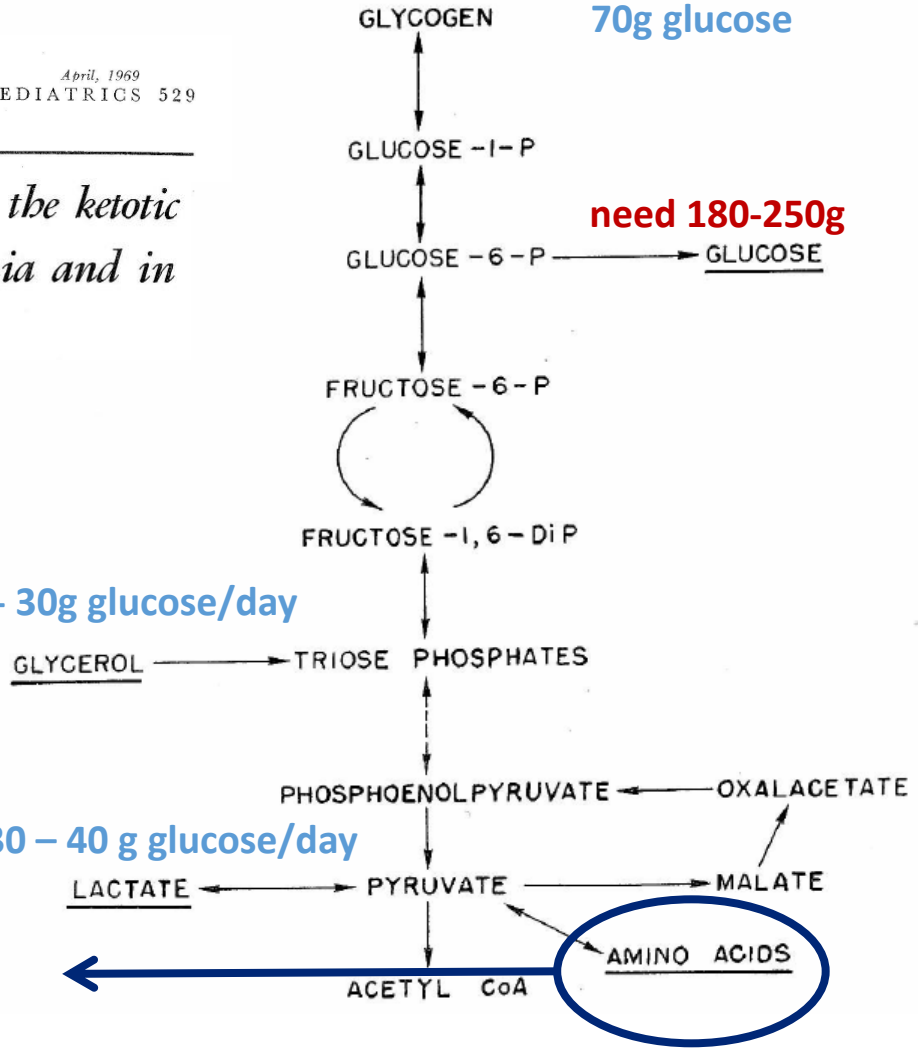
BOSTON, MASS.

April, 1969
The Journal of PEDIATRICS 529

Gluconeogenesis and insulin in the ketotic variety of childhood hypoglycemia and in control children

Glykogenosis type Ia – def glycogenolysis and gluconeogenesis

Enough for 8-10 hours
70g glucose



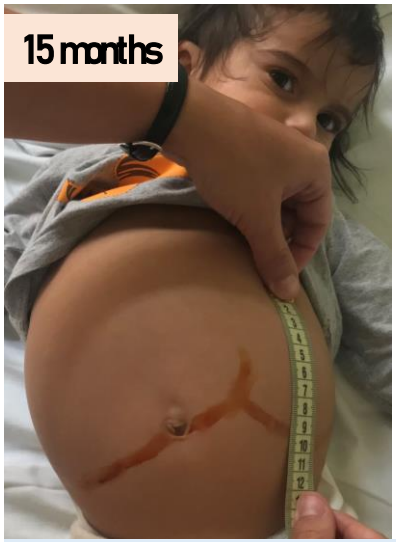
need 180-250g

Create 20 - 30g glucose/day

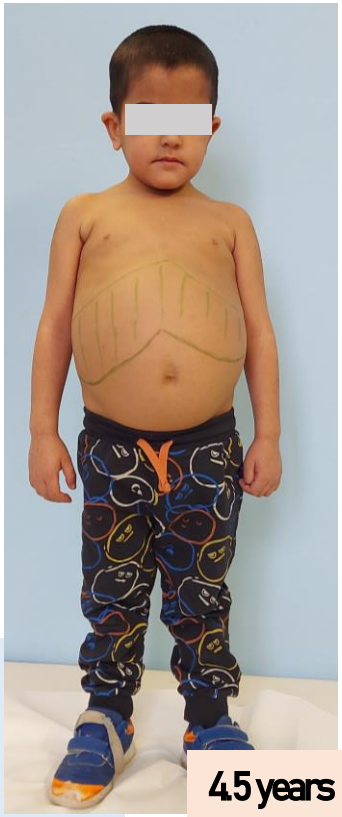
create 30 – 40 g glucose/day

Create 75g glucose/day

Glykogenosis type III



- hepatomegalia
- hepatopathy
- growth failure
- dyslipidemia
- hypoglycemia
- cardiomyopathy/myopathy (GSD IIIa)



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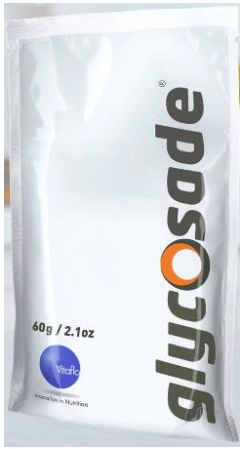
journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Improvement in hypertrophic cardiomyopathy after using a high-fat, high-protein and low-carbohydrate diet in a non-adherent child with glycogen storage disease type IIIa

Burcu Kumru Akin [a,*], Burcu Ozturk Hismi [b], Anne Daly [c]



Summary of publications on dietary intervention and outcomes in GSDIII.

Author/year	Number of patients/ age	Dietary treatment	Outcome
Dagli [7]	1 (23 years)	Protein: 30% Lipid: saturated and carbohydrate: 70%	Cardiomyopathy improved CK levels decreased
Valayannopoulous [8]	1 (2 months)	Protein: 15% Lipid: 65% (with synthetic ketone bodies) Carbohydrate: 20%	Cardiomyopathy improved Insulin and CK levels decreased
Sentner [2]	1 (32 years)	Protein: 37% to 43% Lipid: 2% Carbohydrate: 61%	Cardiomyopathy improved Body mass index decreased
Mayorandan [15]	2 (9, 11 years)	Protein: 7 g/kg/per day Lipid: 8 g/kg/per day Carbohydrate: 0.4 g/ kg/per day	Cardiomyopathy improved CK levels decreased
Brambilla [9]	2 (5, 7 years)	Protein: 25% Lipid: 60% Carbohydrate: 15%	Cardiomyopathy improved CK levels decreased
Francini-Pesenti [16]	1 (34 years)	Protein and lipid: allowed ad libitum with olive oils and medium chain triglyceride Carbohydrate: limited to 20 g/per day	Cardiomyopathy improved CK levels decreased
Marusic [14]	1 (15 years)	Protein: 11% Lipid: 87% Carbohydrate: 2%	Cardiomyopathy improved

Glykogenosis type IX – def fosforylasekinase (PhK)

PhK

Catalytic subunit

γ

muscle isoform *PHKG1*
liver isoform *PHKG2* – GSD IXc

Regulatory subunits

Muscle isoform *PHKA1* – GSD IXd
Liver isoform *PHKA2*, chr. X – GSD IXa

α

PHKB – GSD IXb
var.sval, játra, CNS

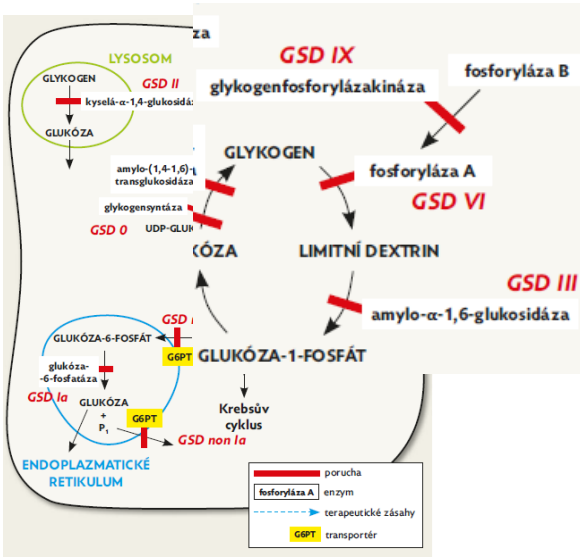
β

CALM1, CALM2, CALM3

δ

Phosphorylation/dephosphorylation

Calcium



Glykogenosis type IX; n=51 patients (45 GSD IXa)

Magner M et al. *in preparation*

Patients 1973-2022

ČR 40x

Chorvatsko 5x

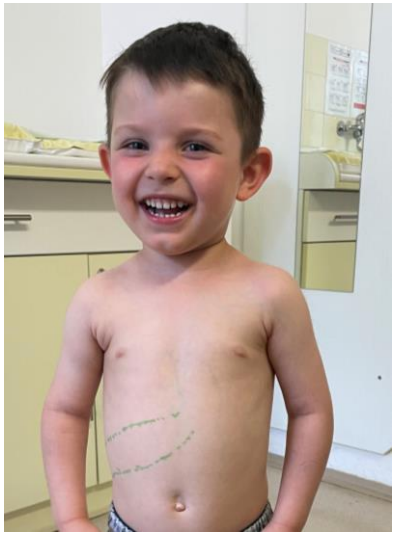
Srbsko 5x

Slovinsko 1x

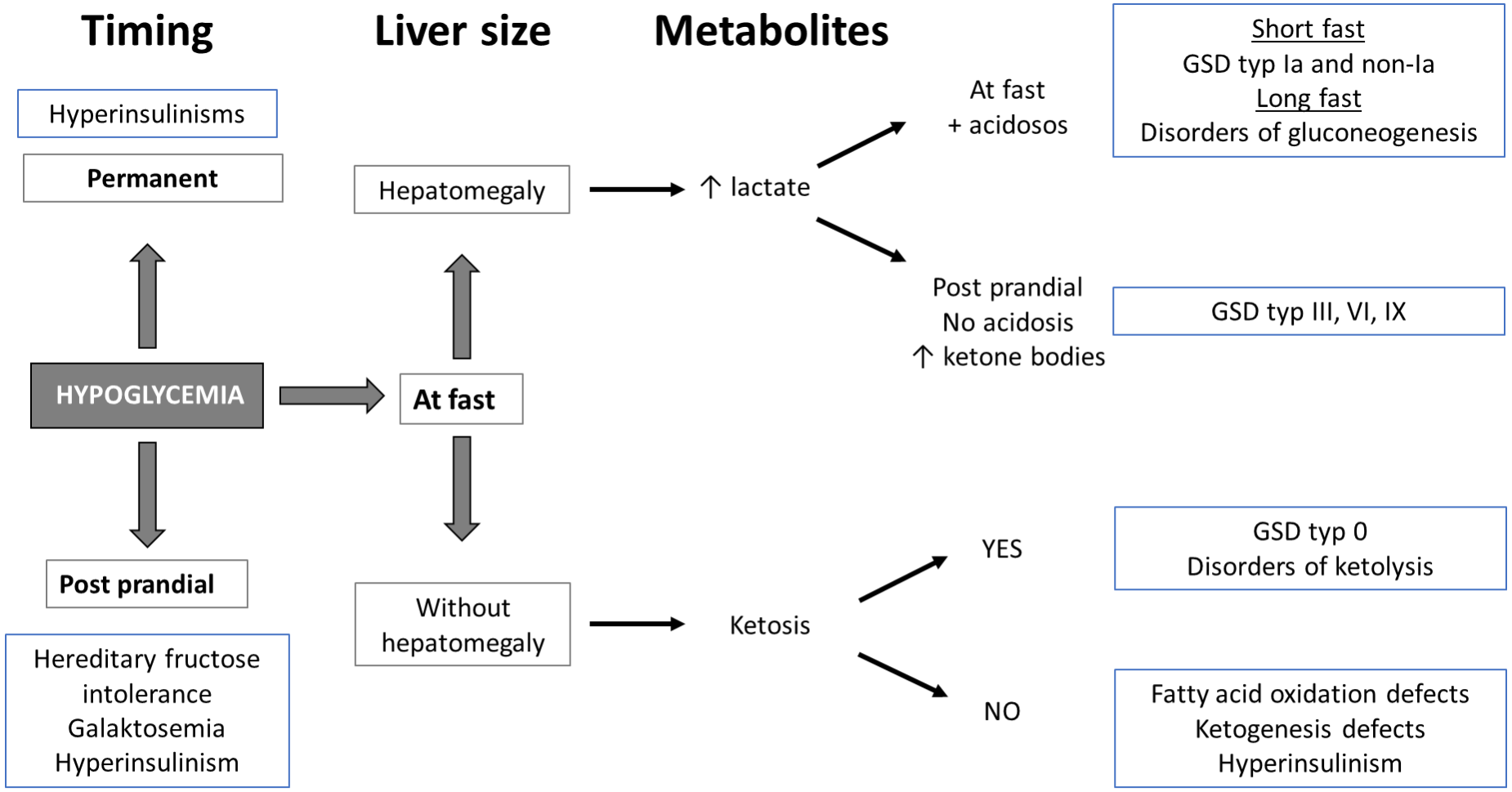
Příznak	Medián	Min/Max
první projev	1,7 let	0-7 let
dg zpoždění	0,5 roku	0-13 let
věk poslední kontroly	14,4 let	1,5-77 let
sledování	8,7 let	0-48,2 let

První příznak	%
hepatomegalie	63
hepatopatie	50
hypoglykemie	23
porucha růstu	17
V době diagnózy	**%**
hepatomegalie	70
∅+4 cm pod oblouk	*0-12 cm*
hepatopatie	87
∅6x nad horní hranici	*0-41x*
hypoglykemie	45
porucha růstu	31

3,5letý chlapec dg. zpoždění 10m
Height 92cm (z-2,42SD)
Liver +5cm
ALT 5,06 ukat/l – infekty ↑25x
AST 4,87 ukat/l
Chol 6,19 mmol/l
TAG 4,78 mmol/l
↓glc po 12h lačnění



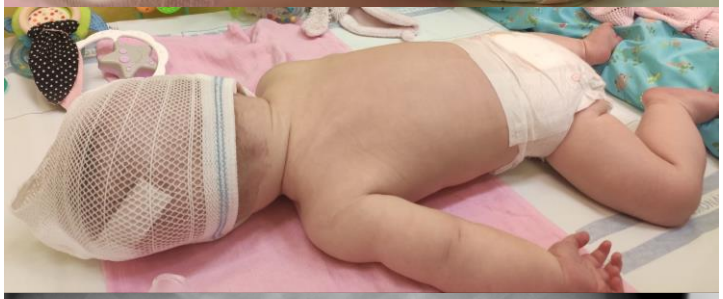
Diagnostic approach to hypoglycemia

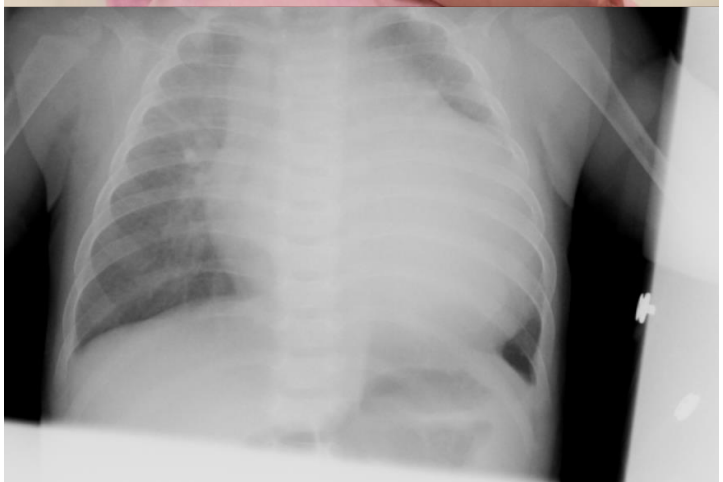


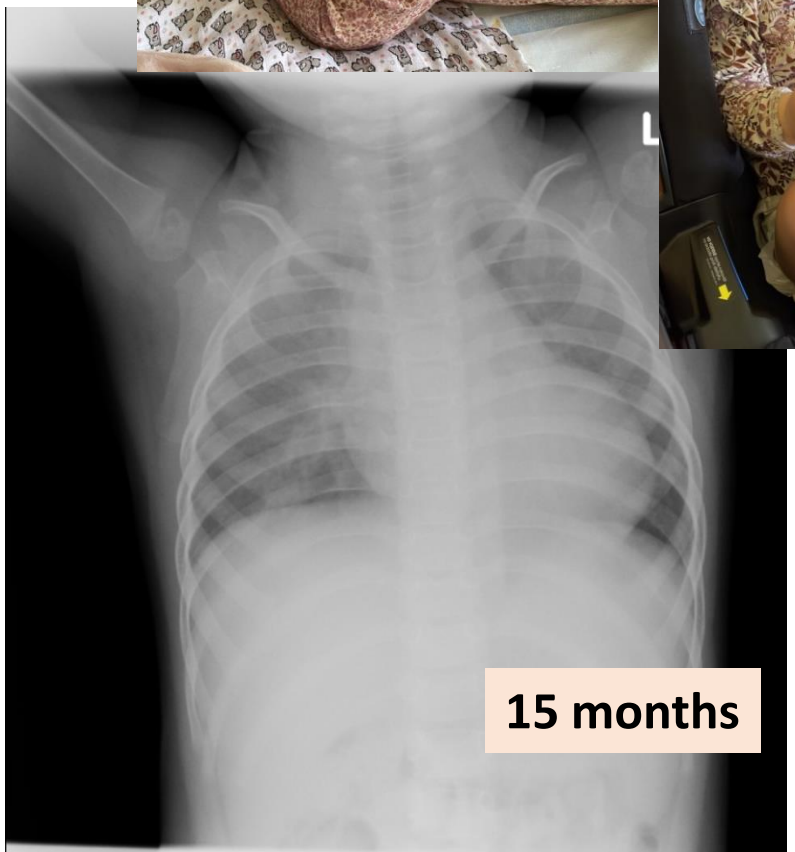
GSD: Glycogen storage disorders

Saudubray, Cazorla, 2016

Pompe disease







Pompe disease – infantile form

A study of 11 children with infantile PD who survived ERT (Prater et al. 2012)

- positive prognostic markers: early initiation of ERT, CRIM+

- improvement of heart parameters and gross motor skills

- complications: nasal speech, residual muscle weakness, ptosis, osteopenia, hearing impairment, dysphagia, risk of arrhythmia

The most successful combination of immunomodulating treatment and ERT in the presence of antibodies:

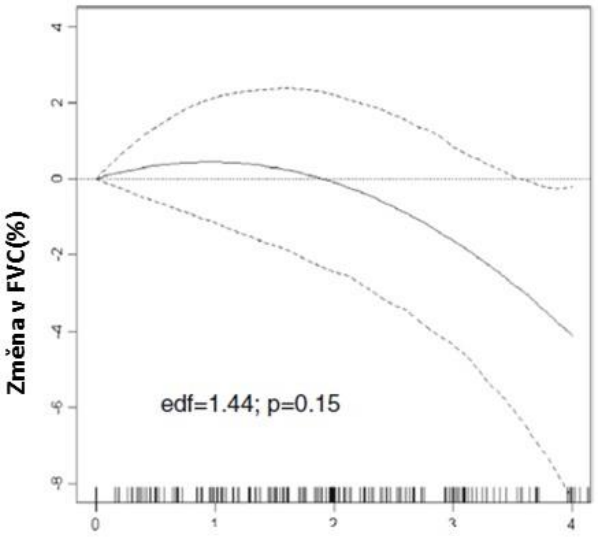
rituximab and metotrexat±IVIG

(Messinger et al. 2012; Mendelsohn et al. 2009)

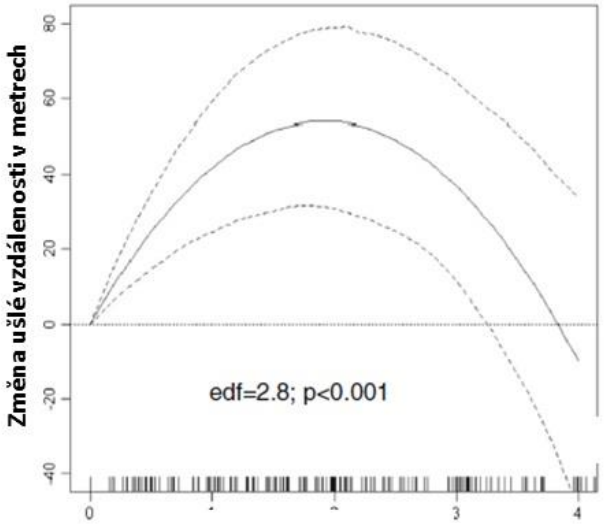
Pompe disease – late onset form

62 adult patients with the late form of Pompe disease

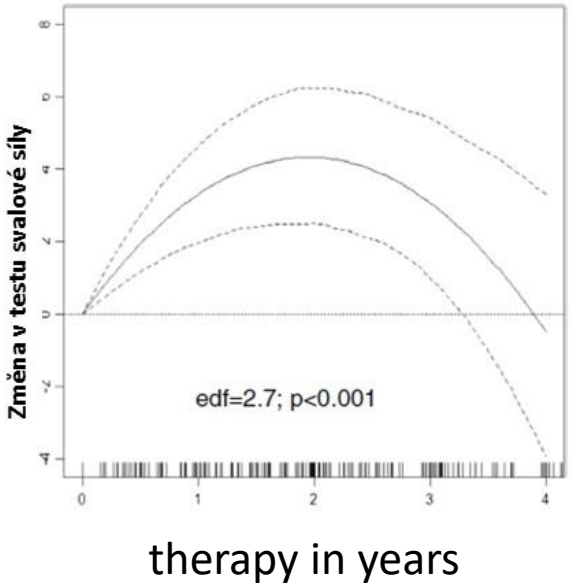
a) FVC(%)



6-minute walk test



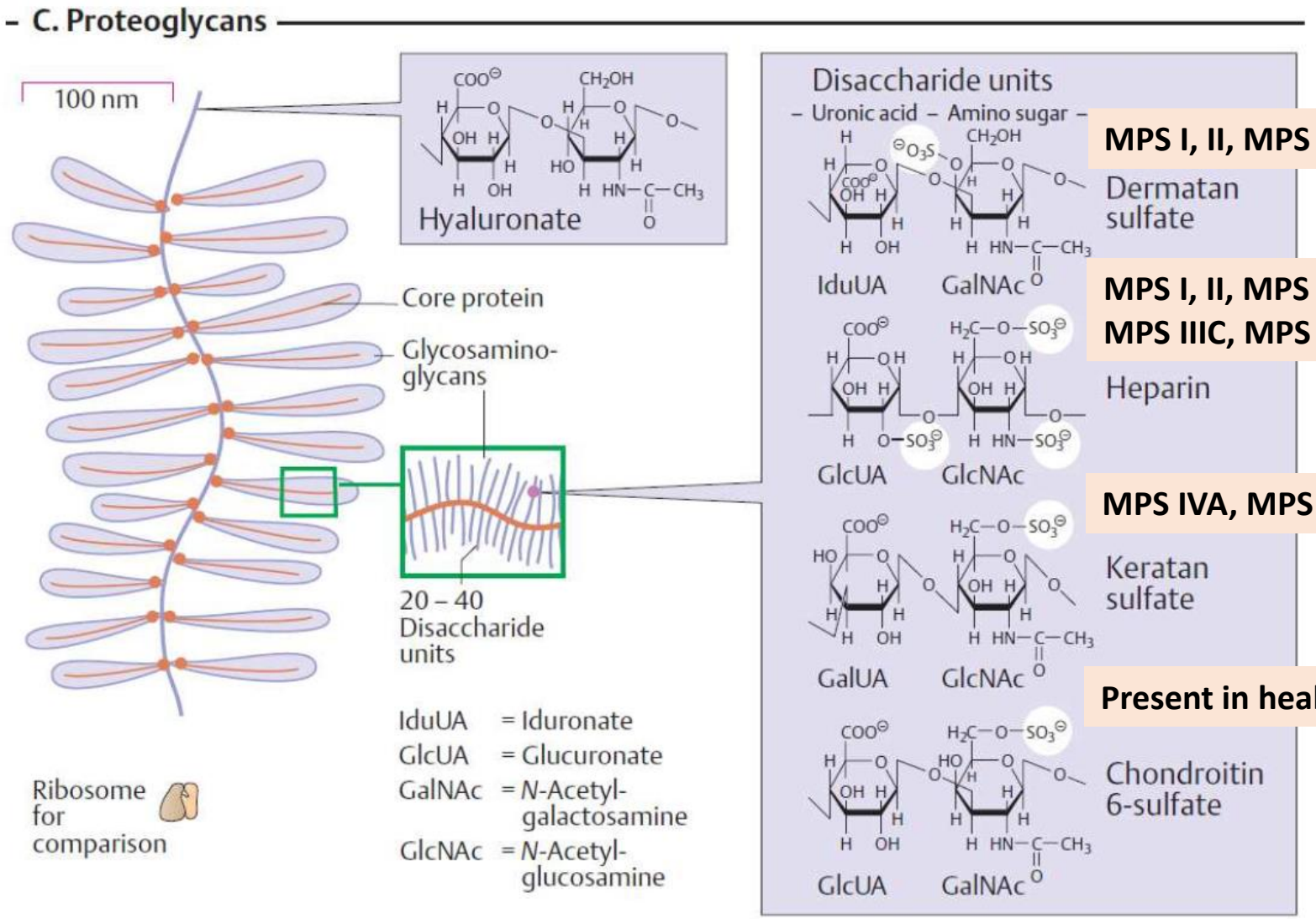
Muscle strength



Improvement in 6-minute walk test and muscle strength ($p < 0.001$) on ERT. Improvement observed in the first two years of treatment.

Anderson et al. *J Inherit Metab Dis,* 2014

Mukopolysaccharidoses (MPS)



MPS I, II, MPS VI, MPS VII

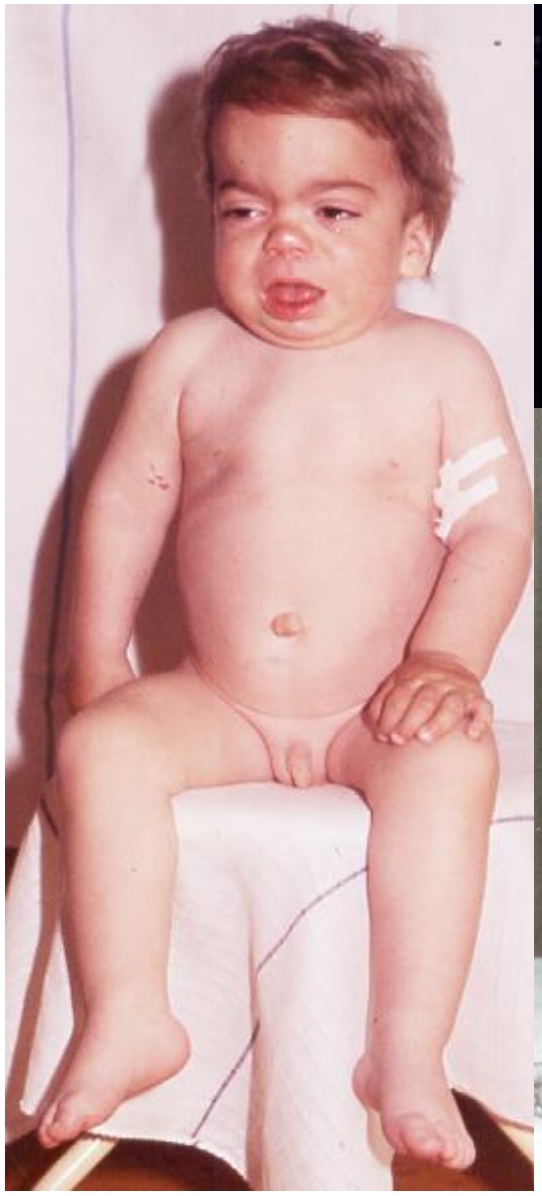
MPS I, II, MPS IIIA, MPS IIIB, MPS IIIC, MPS IIID, MPS VII

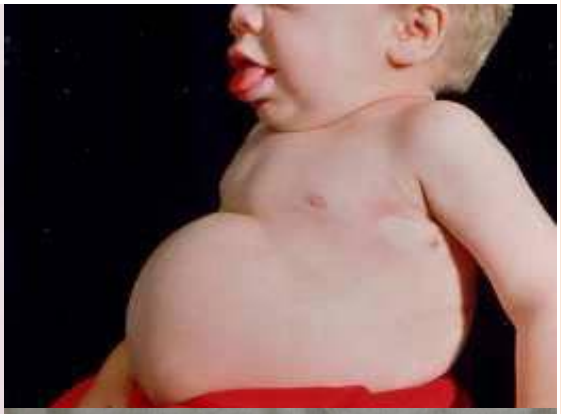
MPS IVA, MPS IVB, MPS IIID

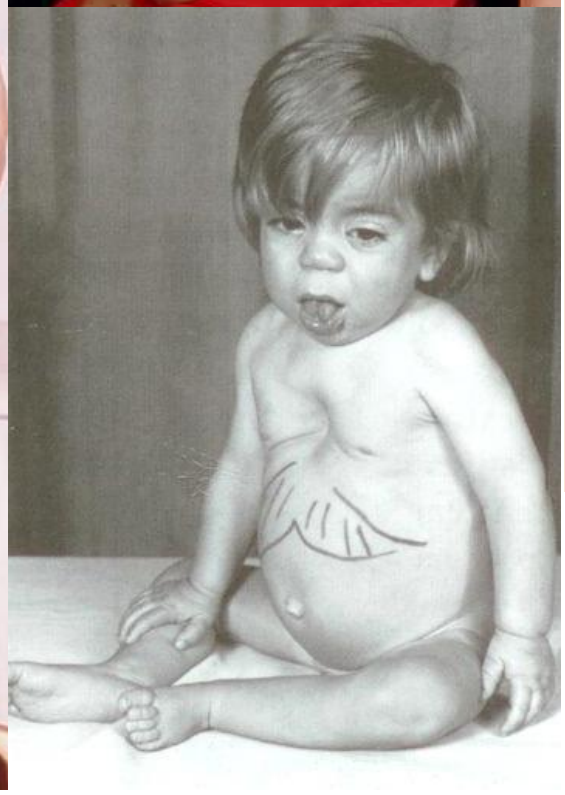
Present in healthy individuals

Koolman J, Röhm KH (2005) *Color atlas of biochemistry, 2nd edition, Thieme*

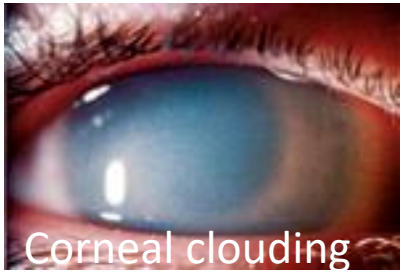
Mukopolysaccharidoses (MPS)

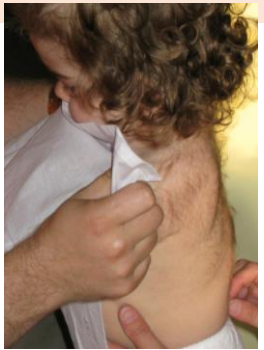




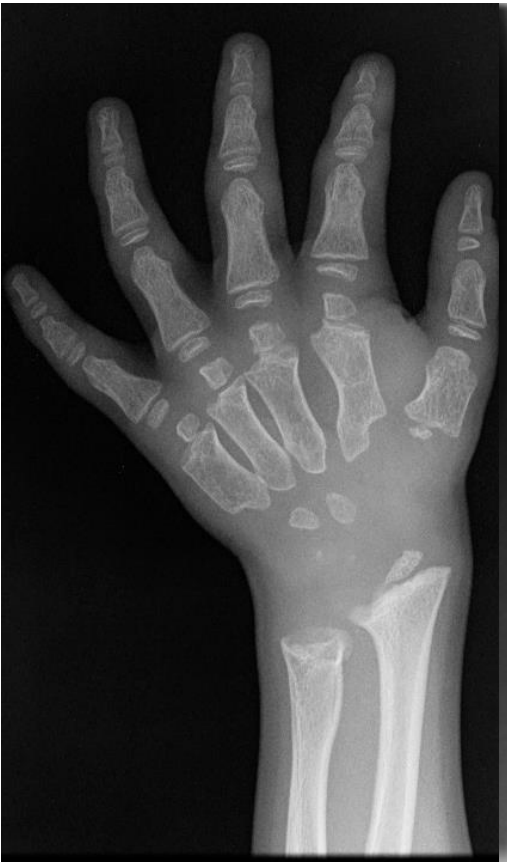


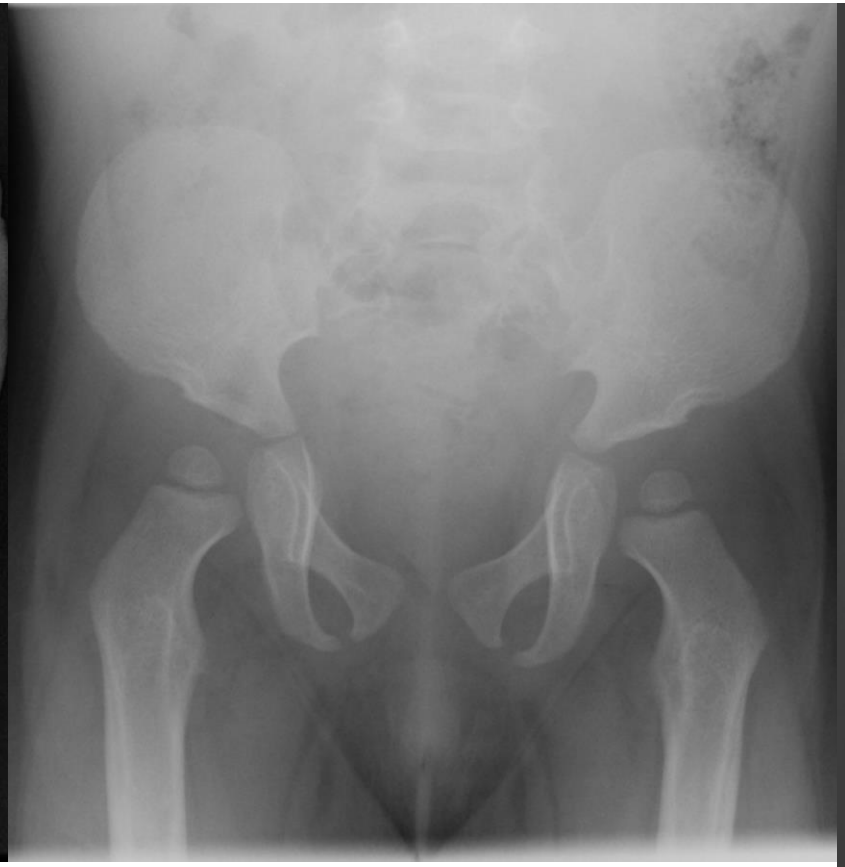
- Macrocephaly
- Frontal bossing
- Coarse facial features
- Bushy eyebrows
- Hypertelorism
- Depressed nasal bridge
- Anteverted nostrils
- Macroglosy
- Gingival hyperplasia
- Pectus excavatum or carinatum
- Umbilical hernia
- Claw hand, wide wrist
- Recurrent mesotitis

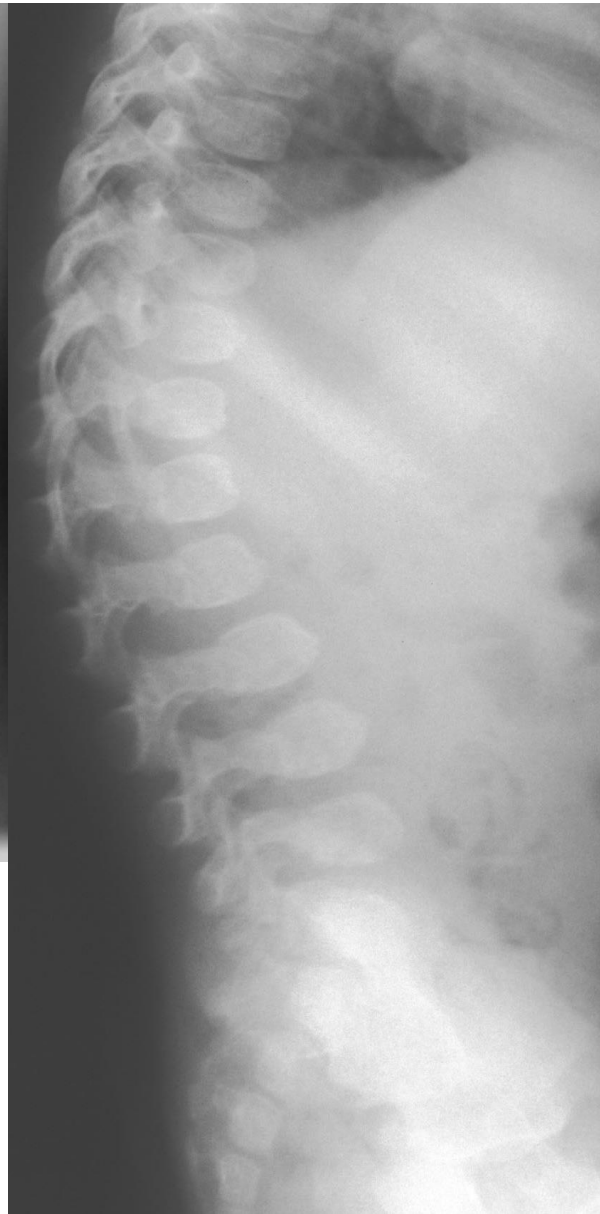




MPS – dysostosis multiplex

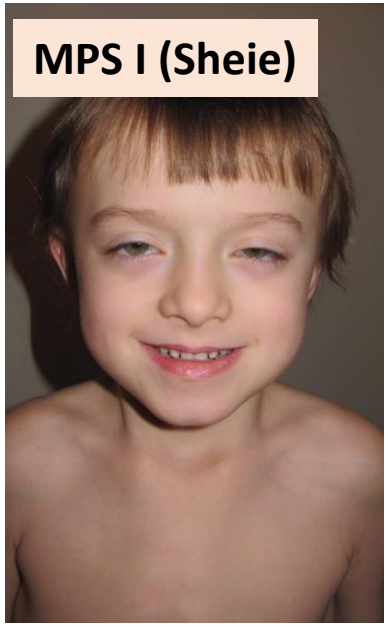


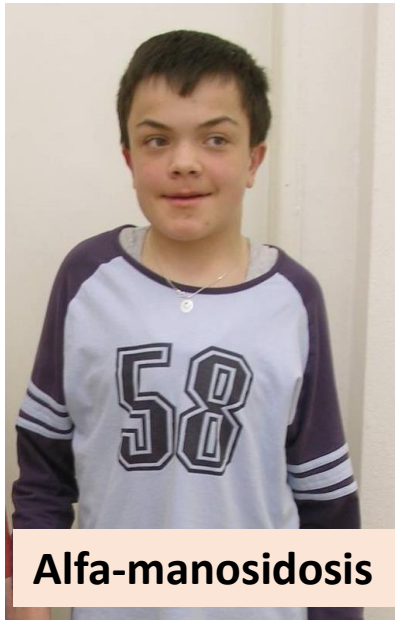


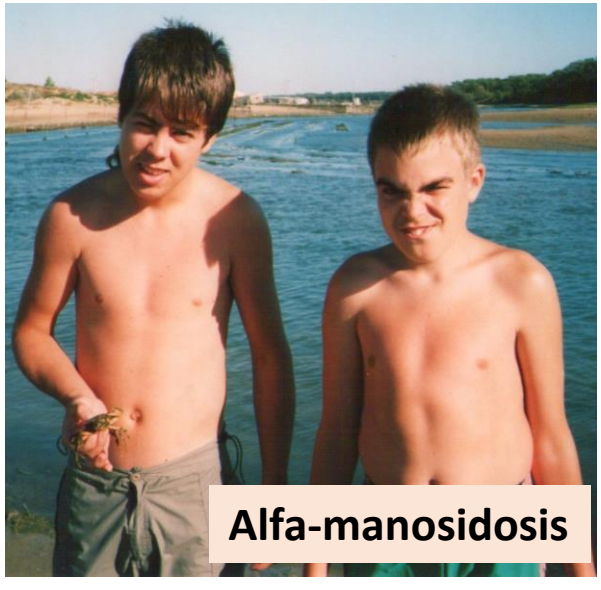


Defective endochondral and membranous growth

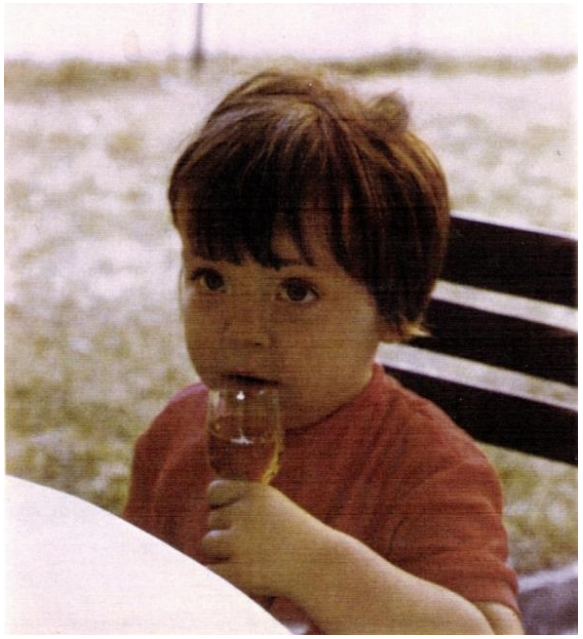
Lysosomal storage disorders

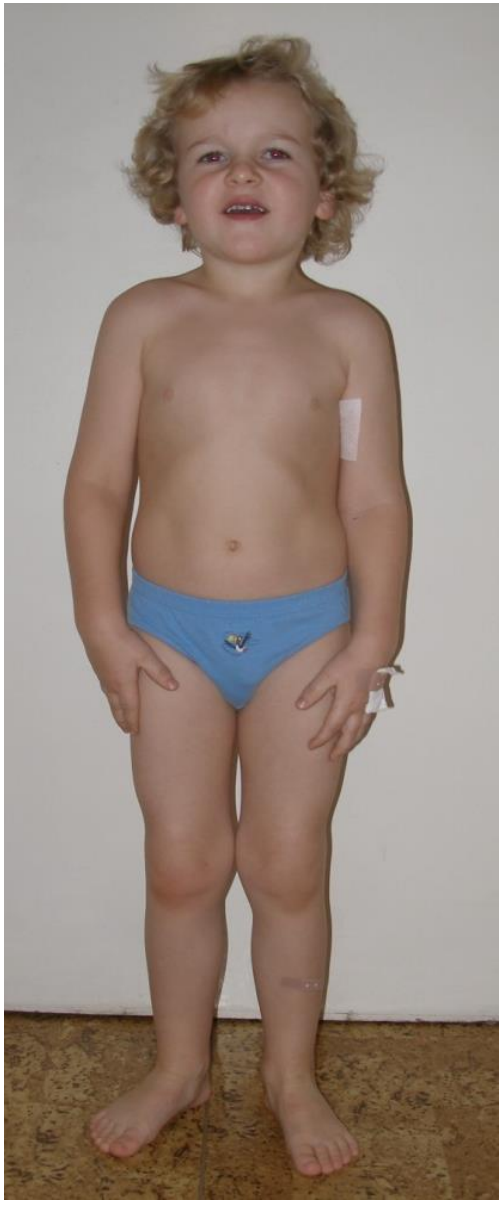


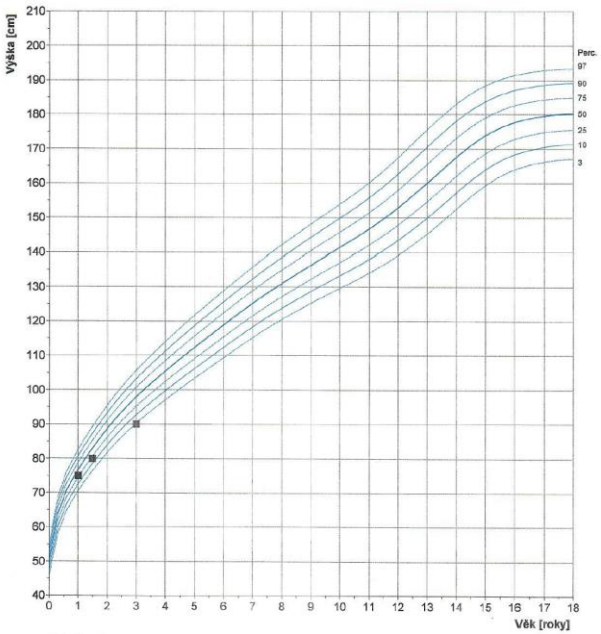


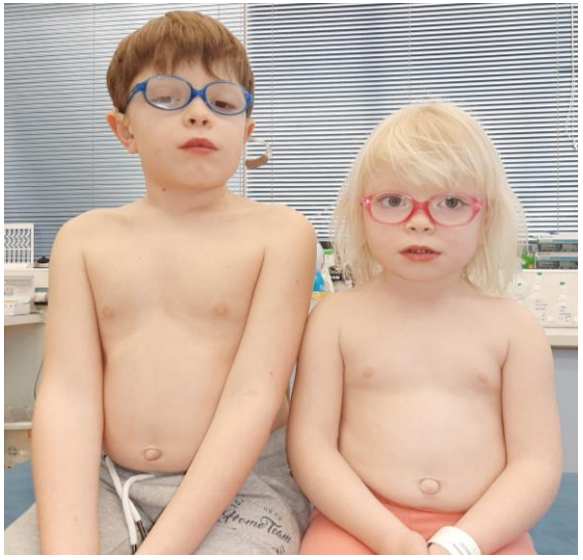


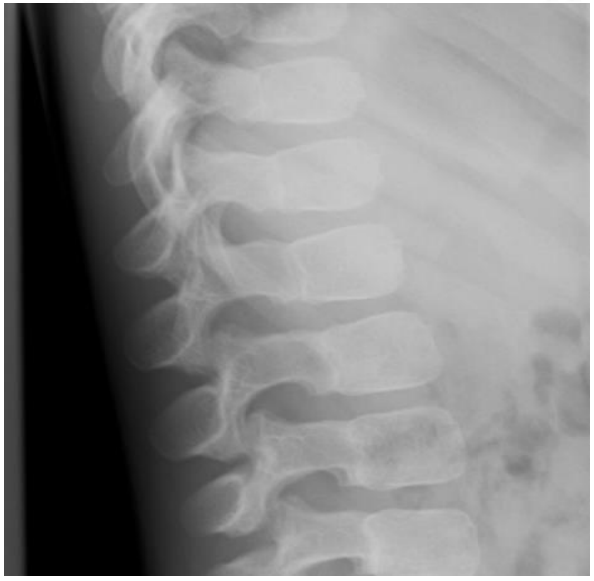
Lysosomal storage disorders











Late diagnosis

1 day

5 months

9 months

11 months

14 months

X-ray spine