

# PATHOPHYSIOLOGY

## Inborn metabolic disorders 1

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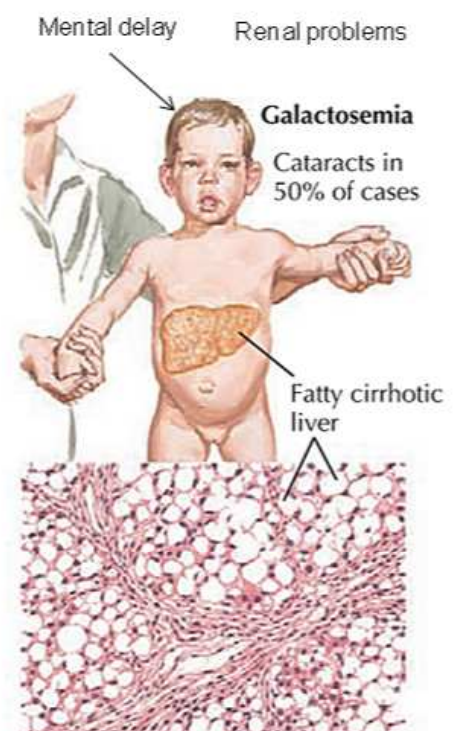
## Disorders of carbohydrate metabolism

### Galactosemia

- Group of AR-disorders caused by defects in the pathway for hepatic conversion of galactose to glucose, Enzymes involved are following:
  - galactokinase (GALK), galactose-1-phosphate;
  - unidyltransferase (GALT),
  - UDP galactose-4-epimerase

### Classic galactosemia (GALT deficiency)

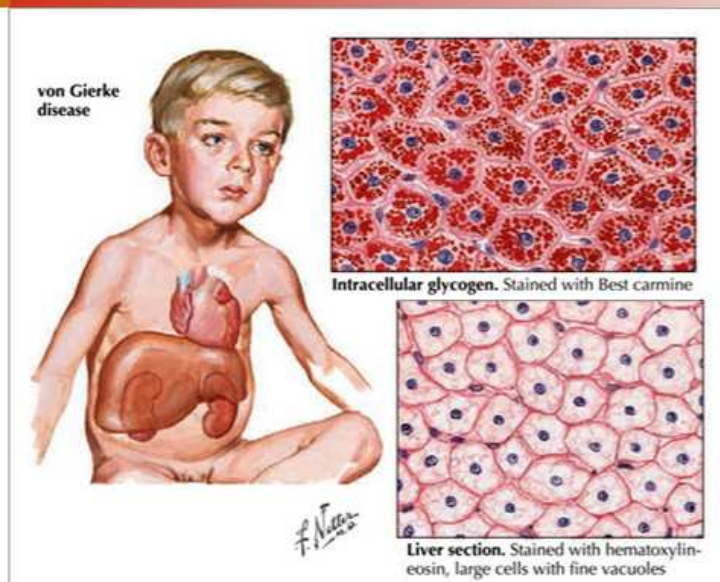
- the most common, the most severe; galactose-1-phosphate cummulates in liver -> resulting in hepatic damage (fatty liver = steatosis; latter fibrotic liver = cirrhosis)
- Cummulates in brain (intellectual impairment; speech delay, learning difficulties) +renal tubules (dysfunction); ovarian failure
- Upon exposure to lactose in milk: vomiting, jaundice, hepatomegaly within a few weeks of birth + may predispose to E.coli sepsis
- Cataracts due to galactitol accumulation in the lens.
- T: lactose-free diet, which
- Dg: galactose-1-phosphate in red blood cells; elevated urine galactitol.







Type	Eponym	Enzyme deficiency	Symptoms
GSD type 0	--	glycogen synthase	Occasional muscle cramping, Hypoglycemia,
GSD type I	<b>von Gierke's disease</b> 1: 50,000- 100,000	glucose-6-phosphatase	Hypoglycemia, Hepatomegaly Growth failure, Lactic acidosis hyperuricemia
GSD type II	<b>Pompe's disease</b> 1 in 40,000	acid alpha-glucosidase	Hepatomegaly, Muscle weakness Death by age ~2 years heart failure
GSD type III	<b>Forbes - Cori's disease</b> 1 in 100,000	glycogen debranching enzyme	Hepatomegaly, Myopathy
GSD type IV	<b>Andersen disease</b>	glycogen branching enzyme	cirrhosis Failure to thrive, death at age ~5 years
GSD type V	<b>McArdle disease</b> 1 in 100,000	muscle glycogen phosphorylase	Exercise-induced cramps Rhabdomyolysis Renal failure by myoglobinuria
GSD type VI	<b>Hers' disease</b> 1 in 65,000- 85,000	liver glycogen phosphorylase	
GSD type VII	<b>Tarui's disease</b>	muscle phosphofructokinase	Exercise-induced muscle cramps and weakness Haemolytic anaemia growth retardation
GSD type IX		phosphorylase kinase, PHKA2	Delayed motor development, Growth retardation
GSD type XI	<b>Fanconi-Bickel syndrome</b>	glucose transporter GLUT2	
GSD type XII	<b>Red cell aldolase deficiency</b>	Aldolase A	Exercise intolerance, cramps
GSD type XIII		$\beta$ -enolase	Increasing intensity of myalgias over decades Serum CK: Episodic elevations Exercise intolerance, cramps



## HEPATIC FORMS

### Glycogen storage disease type I (Von Gierke disease)

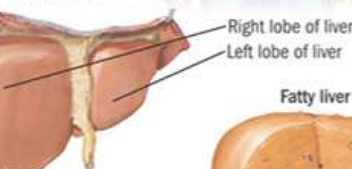
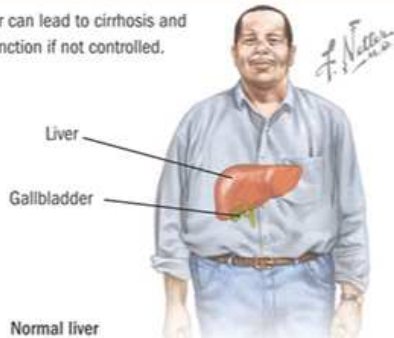
- two subtypes type 1a and type 1b
- clinical hallmarks:
  - neonatal hypoglycemia
  - enlargement of the liver (glycogen accumulation)
  - Intracellular accumulation of glycogen





# HEPATIC FORMS

A fatty liver can lead to cirrhosis and liver malfunction if not controlled.



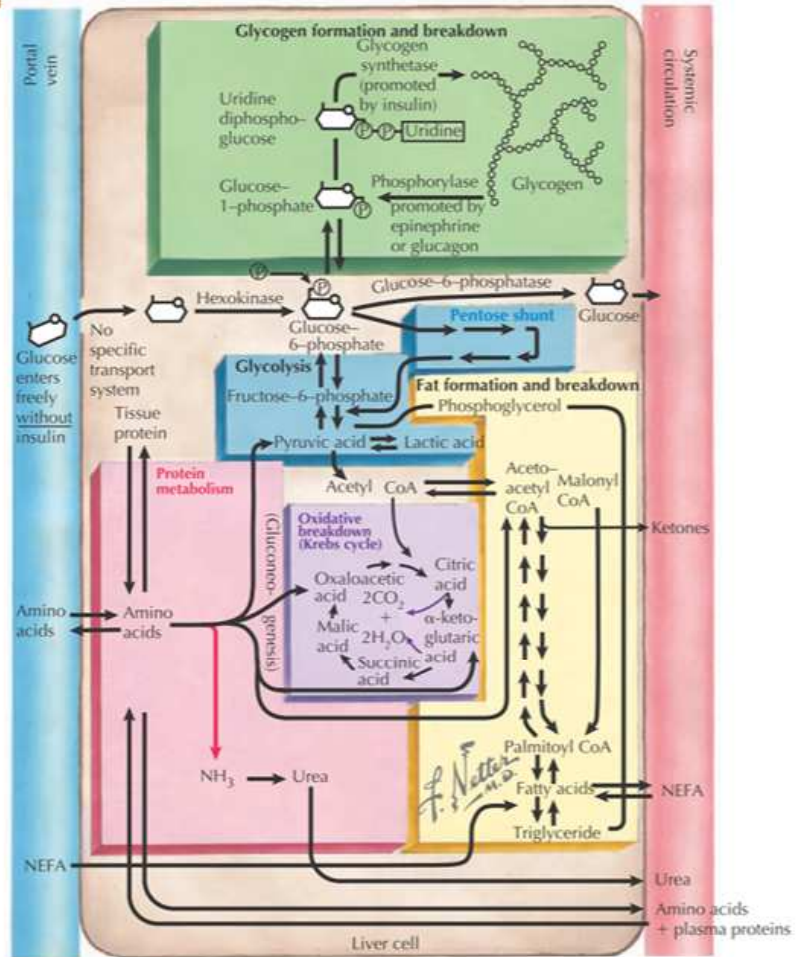
Too much fat in liver cells



Symptoms may include tiredness and belly pain, but often fatty liver is not noticed until a blood test is done.

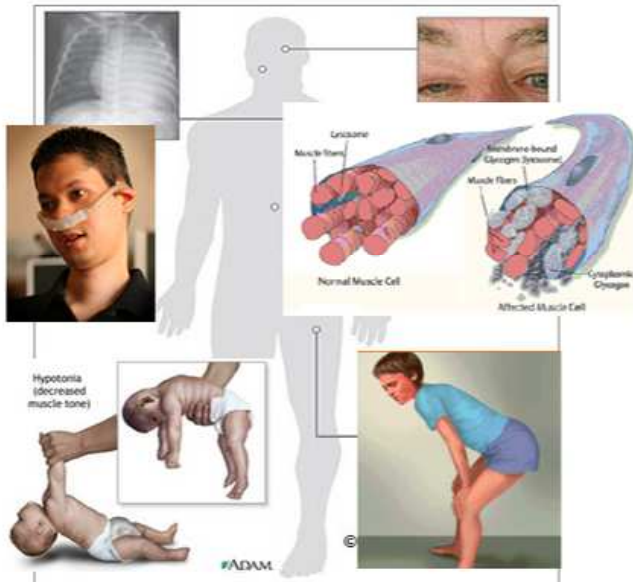


The liver may also be larger than normal.

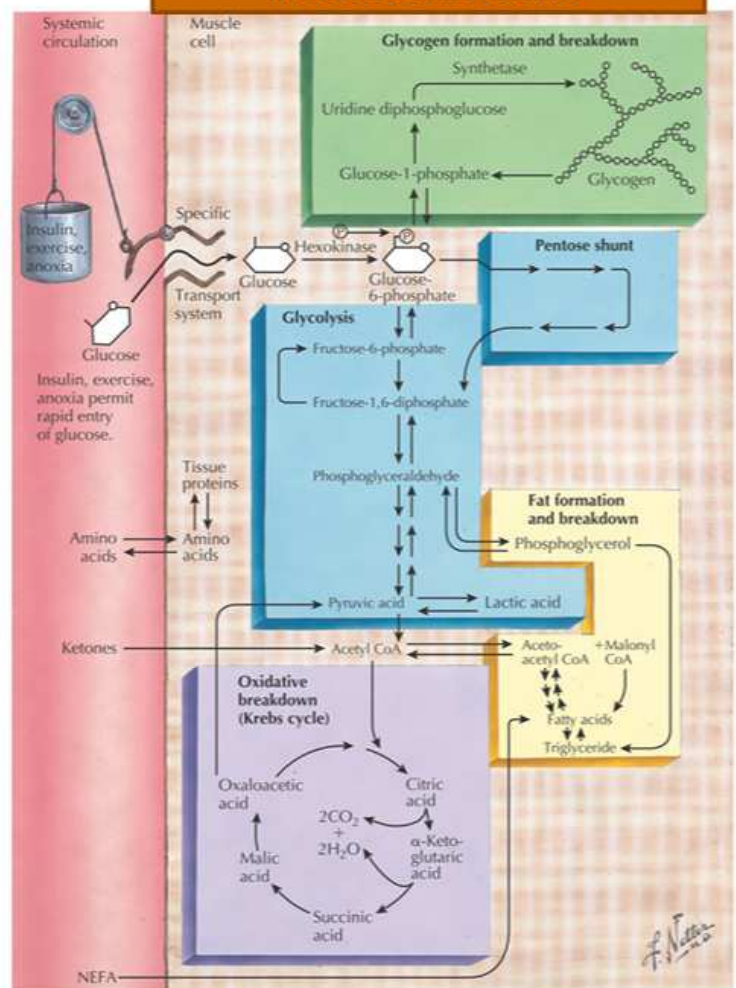


## Glycogen storage disease type II (Pompe's disease; acid maltase deficiency)

- AR; the only glycogen storage disease with a defect in lysosomal metabolism; African Americans: 1: 14,000-40,000; China and Taiwan: most common GSD 1 in 50,000
- first glycogen storage disease identified, in 1932 by the Dutch pathologist J.C.Pompe.
- accumulation of glycogen in skeletal muscles; progressive muscle weakness (myopathy)
- heart, liver and nervous system.



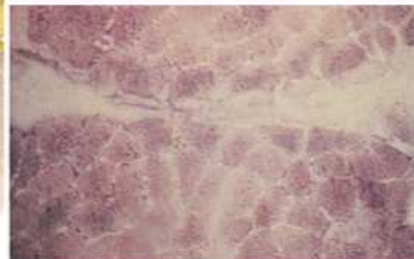
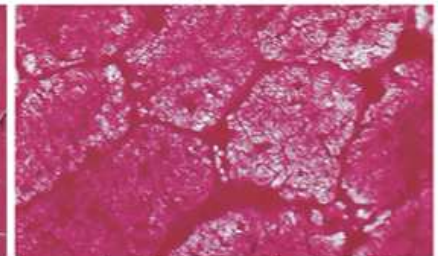
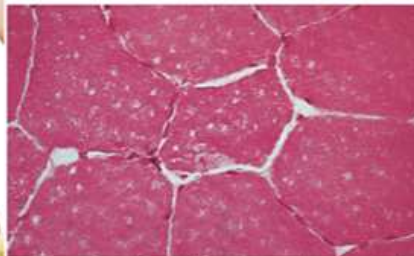
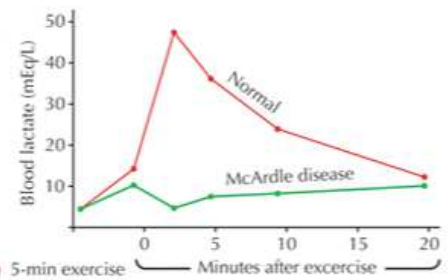
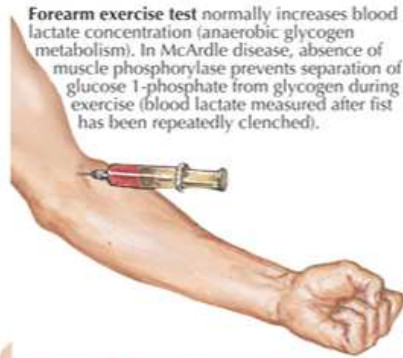
# MUSCULAR FORMS





## McArdle disease (Type V Glycogen Storage Disease)

- GSDs are found in 2-3 children per 100,000 births per year.
- Initial symptoms are cramps, stiffness, fatigue, and pain after exercise
- progressive proximal weakness after exercise
- fixed motor weakness



# Carbohydrate metabolism

## Mucopolysaccharidoses [ICD-10 E76; ICD-9 277.5]

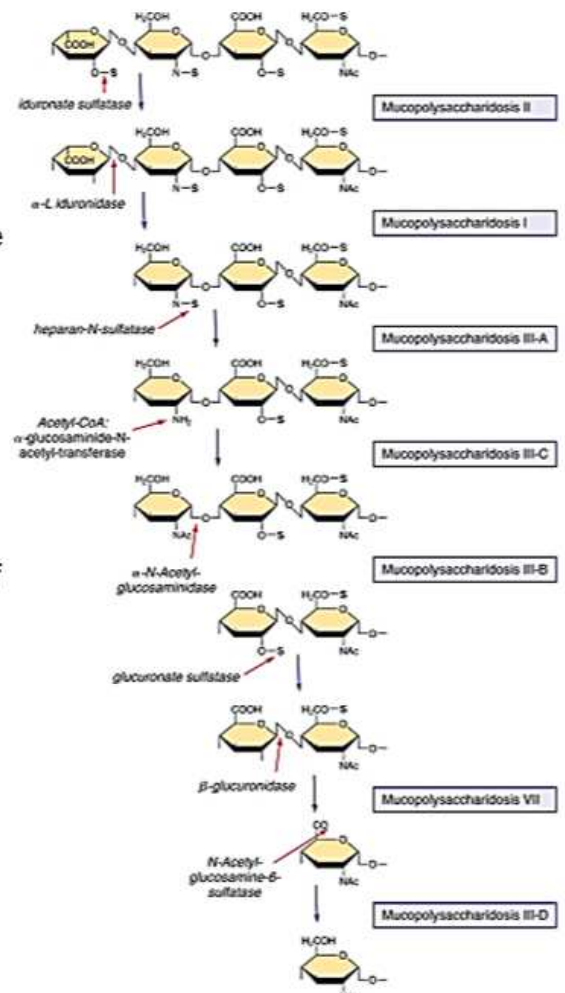
**Df:** metabolic disorders (part of the lysosomal storage disease family) caused by the absence or abnormal function of one of the lysosomal enzymes (altogether 11) involved in breakdown of **glycosaminoglycans** (these collect in the cells, blood and connective tissues) and result in skeletal organ, mental defects

Glycosaminoglycans (formerly mucopolysaccharides) = long chain carbohydrates in ECM (bone, cartilage, tendons, corneas, skin, joints, and loose connective tissue)

**Sy:** Share many clinical features but have varying degrees of severity: May not be apparent at birth but progress as storage of glycosaminoglycans affects bone, skeletal structure, connective tissues, and organs.

- Skeletal abnormalities:** rough facial features (including a flat nasal bridge, thick lips, and enlarged mouth and tongue), short stature with disproportionately short trunk (dwarfism), dysplasia (abnormal bone size and/or shape) and other skeletal irregularities, claw-like hands progressive joint stiffness
- thickened skin, hepatomegaly) splenomegaly), hernias, and excessive body hair growth.

(cont on other slide ->)



Type	Common name /Other names		Gene (Locus) Incidence	Deficient enzyme	Accum. products	Symptoms
MPS IH MPS IS	Hurler syndrome Scheie syndrome Mucopolysaccharidosis type V	AR	IDUA 4p16.3 1:100,000;	$\alpha$ -L-iduronidase	Heparan sulfate Dermatan sulfate	Mental retardation, micrognathia, coarse facial features, macroglossia, retinal degeneration, corneal clouding, cardiomyopathy, hepatosplenomegaly;
MPS II	Hunter syndrome	X	IDS Xq28 1:250,000	Iduronate sulfatase	Heparan sulfate Dermatan sulfate	Mental retardation (similar, but milder, symptoms to MPS I). This type exceptionally has X-linked recessive inheritance
MPS IIIA	Sanfilippo syndrome A 1:280,000	AR	SGSH 17q25.3	Heparan sulfamidase	Heparan sulfate	Developmental delay, severe hyperactivity, spasticity, motor dysfunction, death by the second decade
MPS IIIB	Sanfilippo syndrome B 1:50,000	AR	NAGLU 17q21.2	N-acetylglucosaminidase		
MPS IIIC	Sanfilippo syndrome C	AR	HGSNAT 8p11.21	Heparan- $\alpha$ -glucosaminidase N-acetyltransferase		
MPS IIID	Sanfilippo syndrome D	AR	GNS 12q14.3	N-acetylglucosamine 6-sulfatase		
MPS IVA	Morquio syndrome A	AR	GALNS 16q24.3 1 in 75,000	Galactose-6-sulfate sulfatase	Keratan sulfate	Severe skeletal dysplasia, short stature, motor dysfunction Chondroitin 6-sulfate
MPS IVB	Morquio syndrome B	AR	GLB1 3p22.3	$\beta$ -galactosidase	Keratan sulfate	

MPS VI	Maroteaux-Lamy syndrome	AR	ARSB 5q14.1	N-acetylgalactosamine-4-sulfatase	Dermatan sulfate	Severe skeletal dysplasia, short stature, motor dysfunction, kyphosis, heart def.
MPS VII	Sly syndrome	AR	GUSB 7q11.21 <1:250,000	$\beta$ -glucuronidase	Heparan sulfate Dermatan sulfate	Hepatomegaly, skeletal dysplasia, short stature, corneal clouding, developmental delay Chondroitin 4,6-sulfate
MPS IX	Natowicz syndrome Hyaluronidase deficiency	AR	HYAL1 3p21.31	Hyaluronidase	Hyaluronic acid	Nodular soft-tissue masses around joints, episodes of painful swelling of the masses, short-term pain, mild facial changes, short stature, normal joint movement, normal intelligence

Sy. (cont.)

- **Respiratory infections**, obstructive airway disease and obstructive sleep apnea
- **Heart disease**, enlarged or diseased heart valves.
- **Neurological**: compression of nerves or nerve roots in the spinal cord or in PNS

Sy. (cont.)

- **Sensory: Hearing loss** - conductive (pressure behind the ear drum), neurosensitive (tiny hair cells in the inner ear are damaged); glaucoma and degeneration of the retina
- **Mental**: normal intellect or cognitive developmental delay, or may have severe behavioral problems.



## Hurler syndrome, Hurler's disease Mucopolysaccharidosis type I (MPS I)

- **E:** deficiency of alpha-L iduronidase -> accumulation of heparan sulfate + dermatan sulfate
  - 3 subtypes based on severity of symptoms; MPS I H Hurler syndrome is the most severe; MPS I S or Scheie syndrome and MPS I H-S or Hurler-Scheie syndrome
  - Gertrud Hurler (1889–1965), a German pediatrician; London, work: "A rare disease in two brothers".
- **CM:**
  - symptoms appear during childhood and early death due to organ damage
  - normal at birth ; diagnosis usually made at 6-24 months: hepatosplenomegaly, corneal clouding, skeletal deformities coarse (**gargoyle like**) facies/ prominent forehead, enlarged tongue nasal discharge
  - dwarfism, hunchback, mental retardation, joint stiffness, protuberant abdomen, umbilical and inguinal hernias
  - hearing loss - sensorineural deafness, noisy breathing,
  - cardiac abnormalities coronary artery thickening, angina pectoris



## Hunter syndrome, Mucopolysaccharidosis type II

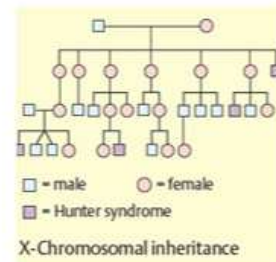
**Df:** iduronate 2-sulfatase deficiency, sulfiduronate sulfatase deficiency, SIDS deficiency, **X-linked recessive**; some cases survive to adulthood

- first described by the Canadian physician Charles H. Hunter (1873-1955)
- two phenotypes: mucopolysaccharidosis type IIA and mucopolysaccharidosis type IIB.

**Oc:** UK 1: 132,000 male births;  
in Israel 1: 34,000.

**Sy:**

- dwarfism, hepatosplenomegaly and a grotesque facies,
- a pigmentary retinopathy with loss of photoreceptors
- cornea is usually clear,
- mental retardation is not always present



4 1/2 years



10 years



13 years



21 years



## Sanfilippo syndrome (MPS-III)

**Df:** rare but severe AR – inherited lysosomal storage disease leading to accumulation of glycosamino-glycan heparan sulfate and manifested mainly by short stature and mental disability..

**Oc:** for all four types combined ~ 1: 70,000 births; There are 4 different types with different enzyme defect

**Sy:**

- motor disability + progressive dementia,
- aggressive behavior, hyperactivity, seizures,
- deafness and loss of vision
- inability to sleep for more than a few hours at a time.



## Maroteaux-Lamy disease (MPS VI)

**Df:** severe to mild AR dis, with somatic involvement seen in MPS I, but with good intelligence.

**Et:** mutations of the ARSB gene (5q11-13 encoding N-acetylgalactosamine-4-sulfatase (arylsulfatase B).

**Sy:** Severe: growth can be normal for the 1st few years

corneal clouding, coarse facial features, joint stiffness, valvular heart disease, hydrocephalus, and dysostosis multiplex

Mild: Spinal cord compression thickening of the dura in the upper cervical canal with resultant myelopathy



## Morquio syndrome (MPS IV)

**Df:** very rare AR- dis. with 2 types caused by defect of galactose 6-sulfate sulfatase (Type A) or beta-galactosidase (Type B); onset 1- 3 year

**Sy:** progressive skeletal changes: start at age of 18 months, stops completely by the age of 8; severe forms may not live > 20.30 y.

- Dwarfism; bell-shaped chest, flattening or curvature of the spine, shortened long bones, dysplasia of the hips, ankles and wrists, knock-knee, joint stiffness,
- Conductive and/or neurosensitive deafness, corneal clouding intelligence normal;
- Odontoid hypoplasia = defect in bones between the head and neck (need fusion)
- Restricted breathing, and heart disease <- spatial restriction





# Comparisons of various MPS - forms

Jürgen Spranger, J.: *Mucopolysaccharidoses*. Chapter 88. In: *Nelson Textbook of Pediatrics*, 18th ed., Kliegman (Ed), 2007



**Hurler syndrome (MPS I-H)**  
Marked dwarfism with protruding abdomen, hepatosplenomegaly, coarse facies, and umbilical hernia, joint contractures (hips, knees, elbows), mental retardation, corneal clouding (above), and cardiac anomalies. Usually fatal by ages 6 to 12. Autosomal recessive.

**Hunter syndrome (MPS II)**  
Dwarfism less severe than in Hurler's syndrome; hepatosplenomegaly and umbilical hernia. Corneal clouding can occur late in childhood; intelligence may be normal. Life expectancy, adulthood. X-linked recessive.



MANIFESTATIONS	MUCOPOLYSACCHARIDOSIS TYPE						
	I-H	I-S	II	III	IV	VI	VII
Mental deficiency	+	-	±	+	-	-	±
Coarse facial features	+	(+)	+	+	-	+	±
Corneal clouding	+	+	-	-	(+)	+	±
Visceromegaly	+	(+)	+	(+)	-	+	+
Short stature	+	(+)	+	-	+	+	+
Joint contractures	+	+	+	-	-	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	-	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

Various types of mucopolysaccharidoses. I: Hurler disease, 3 yr; II: Hunter disease, 12 yr; III: Sanfilippo disease, 4 yr; IV: Morquio disease, 10 yr; VI: Maroteaux-Lamy disease, 15 yr



MPS-I



MPS-II



MPS-III



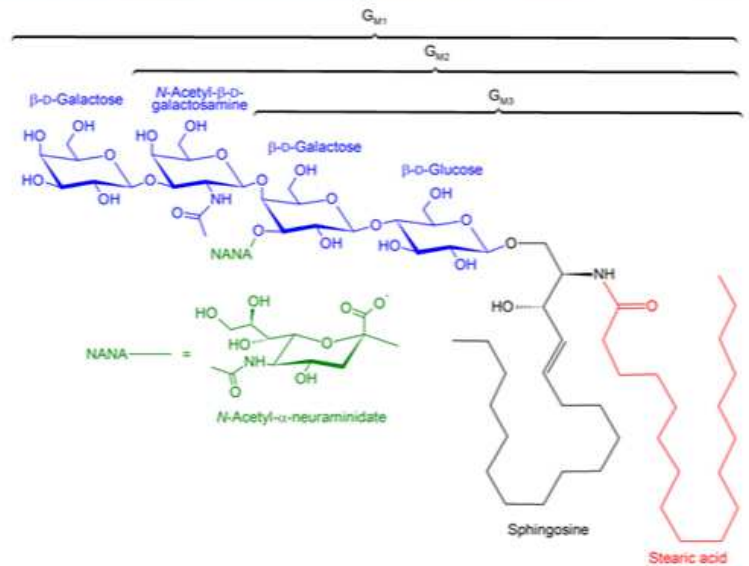
MPS-IV



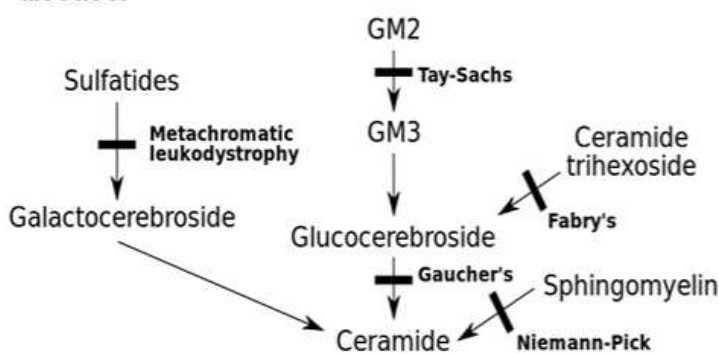
MPS-VI

## Lipid storage disorders

**Ganglioside** = GM1-3, GD1-3, GT1-3  
 glycosphingolipid (ceramide and oligosaccharide)  
 with one or more sialic acids (e.g. n-acetylneuraminic acid, NANA) linked on the sugar chain; Present on cell surfaces (ceramide in membrane) oligosaccharides located on the extracellular surface CNS 6% of all phospholipids; cell-to-cell communication;



- **Lipid storage disorder (lipidosis)** - group of inherited metabolic disorders characterized by pathological accumulation of lipids (buildup of fats) in body's cells and tissues (brain, peripheral nervous system, liver, spleen and bone marrow).
- **Etio:** inherited malfunction or deficiency of lysosomal enzymes needed to metabolize;
  - a) AR – inheritance; 25% chance of defect; 50% chance of being a carrier, 25% healthy
  - b) X-linked recessive Boys 50% chance of inheriting the disorder. Daughters have a 50%
- **Class:** a) sphingolipidoses (sphingolipid metabolism); b) other: fucosidosis, Schindler disease Wolman disease.



## Sphingolipidoses

- Gangliosidosis
  - GM1 gangliosidoses
    - Niemann-Pick disease
  - GM2 gangliosidoses
    - Tay-Sachs disease
    - Sandhoff disease
    - GM2-gangliosidosis
- Glycolipidoses
  - Globosidosis
    - Fabry's disease
  - Krabbe disease
  - Metachromatic leukodystrophy
- Sphingomyelinosis
  - Niemann-Pick disease (
- Glucocerebroside
  - Gaucher's disease
- Sphingosinosis
  - Farber disease





# Sphingolipidoses

Disease	Deficient enzyme	Accumulated products <sup>1</sup>	Symptoms
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin (brain, erythrocytes)	<b>Autosomal recessive</b> ; 1:100,000 Mental retardation, Spasticity, Seizures Hepatosplenomegaly, Thrombocytopenia, Ataxia
Fabry disease	$\alpha$ -galactosidase A	Glycolipids, particularly ceramide trihexoside, in brain, heart, kidney	<b>X-linked</b> , 1:40,000 to 1:120,000 Infarction in affected organs; Acroparesthesia Angiokeratomas, Hypohidrosis
Krabbe disease	Galactocerebrosidase	Glycolipids, particularly galactocerebroside, in oligodendrocytes	<b>Autosomal recessive</b> ; 1:100,000 Spasticity, Neurodegeneration (leading to death) Hypertonia, Hyperreflexia, Decerebration-like posture, Blindness, Deafness
Gaucher disease	Glucocerebrosidase	Glucocerebroside in RBCs, liver and spleen	<b>Autosomal recessive</b> ; 1:20,000 births Hepatosplenomegaly, Pancytopenia Bone pain, Erlenmeyer flask deformity
Tay-Sachs disease	Hexosaminidase A	GM2 gangliosides in neurons	<b>Autosomal recessive</b> ; 1:320,000 Neurodegeneration, Developmental disability Early death
Metachromatic leukodystrophy (MLD)	Arylsulfatase A or prosaposin	Sulfatide compounds in neural tissue	<b>Autosomal recessive</b> 1:40,000 to 1:160,000 Demyelination in <u>CNS</u> , <u>PNS</u> ; Mental retardation Motor dysfunction Ataxia Hyporeflexia Seizures

## Disorders of lipid metabolism

### Gaucher disease ( Gaucher splenomegaly)

1882 French physician Philippe Gaucher; 1965, confirmed genetic mechanism

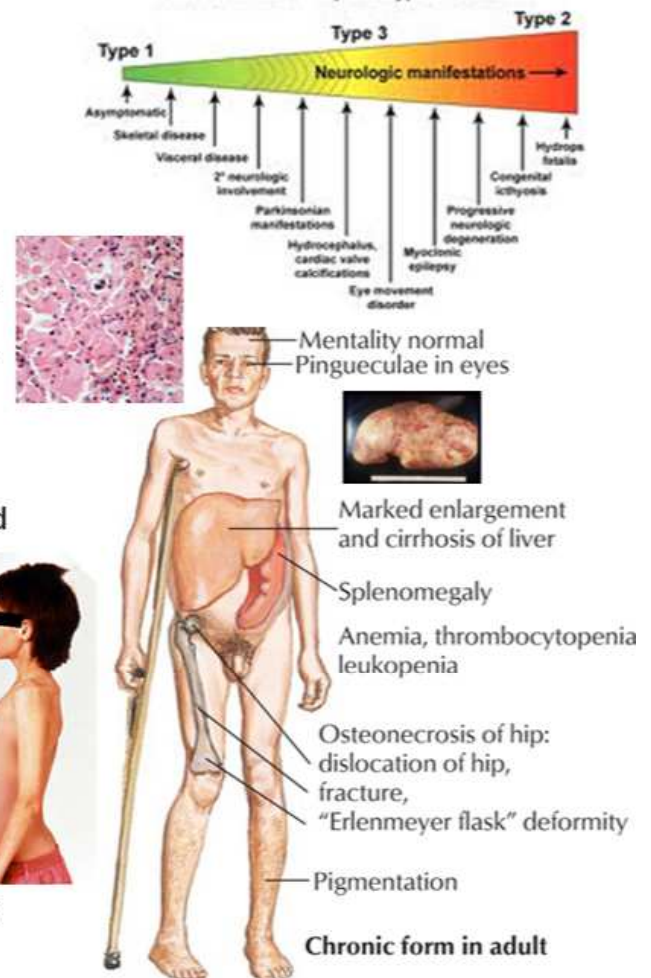
- **Type 1 GD** Non-neuropathic ; most common lipid met. Dis.; anytime in childhood or adulthood.
- **Type 2 GD** acute neuropathic form : brain, cord. fatality high; begin within 6 months of life
- **Type 3 GD** chronic neuropathic type: progresses slowly; any time in infancy or childhood.
- **Type 4 GD** perinatal lethal form ; most severe
- **Type 5 GD** cardiovascular type ;

Oc.: Type 1 : 1: 50,000 live births; (Ashkenazi Jews) Type 2 and 3 1: 100,000 births

Sy.:

- Abnormal enlargement of the spleen and liver ( hepat-splenomegaly) + abd press; liver cirrhosis; icterus
- Anemia; trombocytopenia (easy bruising)
- Leukocytopenia (risk of infection)
- Pulmonary discomfort; Osteoporosis; Arthritis
- Seizures, Mental disability, Increased muscle tone
- Muscle twitching Failure to thrive (observed in Type 2)
- Difficulty swallowing, Abnormal ocular movements, including squint

Gaucher Disease - a phenotypic continuum





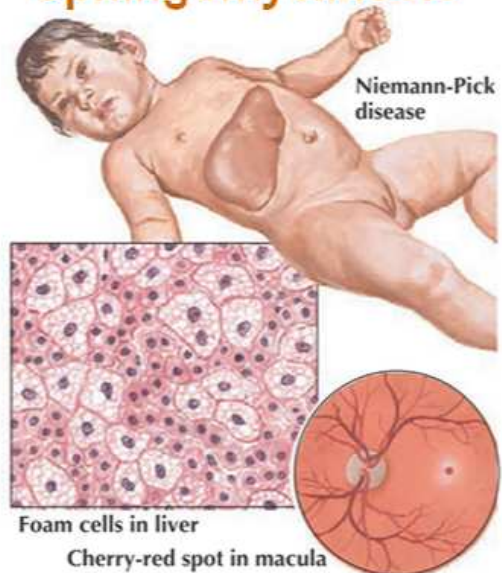
## Niemann-Pick disease

**Def:** group of severe metabolic disorders manifested by sphingomyelin accumulation in lysosomes of various cells and tissues causing their enlargement and damage

**Clin:**

- hepatomegaly -> reduced appetite, abdominal distension pain.
- splenomegaly (enlarged spleen) -> thrombocytopenia
- cerebellum -> unsteady gait (ataxia), slurring of speech (dysarthria) and dis-coordinated swallowing (dysphagia).
- basal ganglia -> abnormal posturing of the limbs, trunk, and face (dystonia).
- brainstem -> impaired voluntary rapid eye movements (supranuclear gaze palsy).
- cerebral cortex -> loss of intellectual abilities, dementia and seizures.

## Sphingomyelinosis



*Resources:*

*Niemann-Pick disease Types A and B - causes, symptoms, diagnosis, treatment, pathology;*

<https://www.youtube.com/watch?v=RCOvoa4idyA>

*Niemann-Pick disease Type C - causes, symptoms, diagnosis, treatment, pathology*

<https://www.youtube.com/watch?v=Fx28WYe-OW8>

## GM2 myelinosis

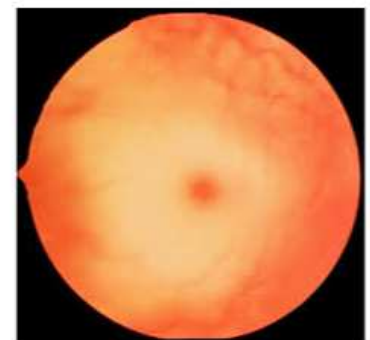
- **Tay-Sachs disease** destruction of nerve cells in the brain and spinal cord; **Early** 3-5 months; psychomotor degradation (losing ability to turn over, sit, or crawl; seizures, hearing loss, and inability to move, death 4y ; **juvenile** (death by age 15) or **late-onset** is less severe.

*Resources:*

*Tay-Sachs disease - causes, symptoms, diagnosis, treatment,*

[https://www.youtube.com/watch?v=2z3nSnBe8Vg&list=PLYUfYO5M](https://www.youtube.com/watch?v=2z3nSnBe8Vg&list=PLYUfYO5M87dXTD1n0BrgLjk3DjXJ-IPQ5)

[87dXTD1n0BrgLjk3DjXJ-IPQ5](https://www.youtube.com/watch?v=2z3nSnBe8Vg&list=PLYUfYO5M87dXTD1n0BrgLjk3DjXJ-IPQ5)



*Fabry disease - causes, symptoms, diagnosis, treatment, pathology*

<https://www.youtube.com/watch?v=AUkqYvZ9tn0>

# Fatty-acid metabolism disorders (FAOD)

- Carnitine Transport Defect
- Carnitine-Acylcarnitine Translocase (CACT) Deficiency
- Carnitine Palmitoyl Transferase I & II (CPT I & II) Deficiency
- 2,4 Dienoyl-CoA Reductase Deficiency
- Electron Transfer Flavoprotein (ETF) Dehydrogenase Deficiency (GAII & MADD)
- 3-Hydroxy-3 Methylglutaryl-CoA Lyase (HMG) Deficiency
- Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCAD deficiency)
- Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency (LCHAD deficiency)
- Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD deficiency)
- Short-chain acyl-coenzyme A dehydrogenase deficiency (SCAD deficiency)
- 3-hydroxyacyl-coenzyme A dehydrogenase deficiency (M/SCHAD deficiency)

**Aminoaciduria**



## Phenylketonuria

- **Def:** Inherited disorder of phenylalanine metabolism
- **Etio:** AR, deficiency of phenylalanine hydroxylase 12q24.1 >1000 associated mutations
- **Epi:** 1:10,000 (European), 1:50,000 (African)
- **Clin:** Odor ("Musty"), Eczema,
- Brain accumulation of phenylalanin -->tremor
- developmental delay

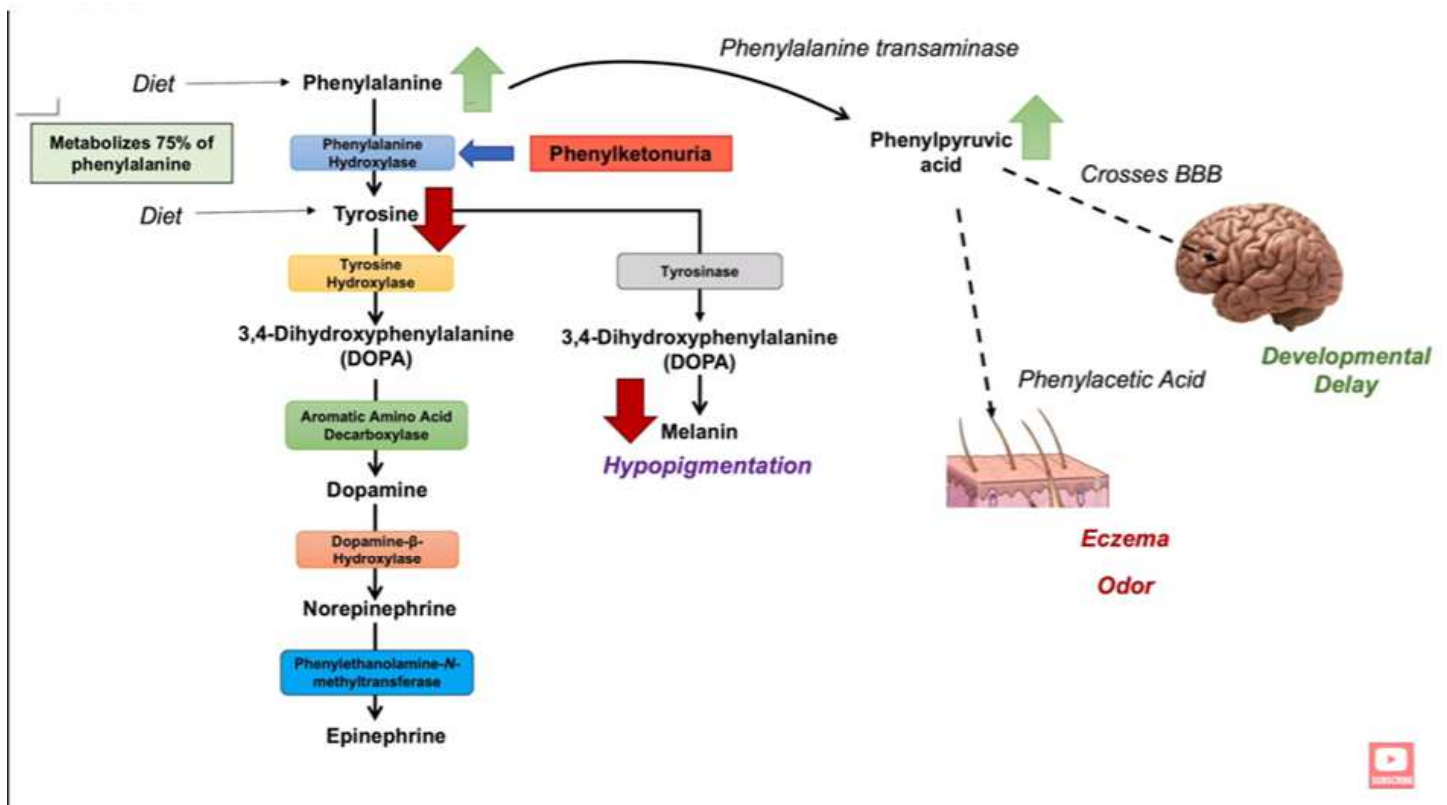
*Phenylketonuria - causes, symptoms, diagnosis, treatment, pathology*

<https://www.youtube.com/watch?v=HYgOld-C0uQ>

*Phenylketonuria (PKU)*

<https://www.youtube.com/watch?v=mBNRuNsDJKU>

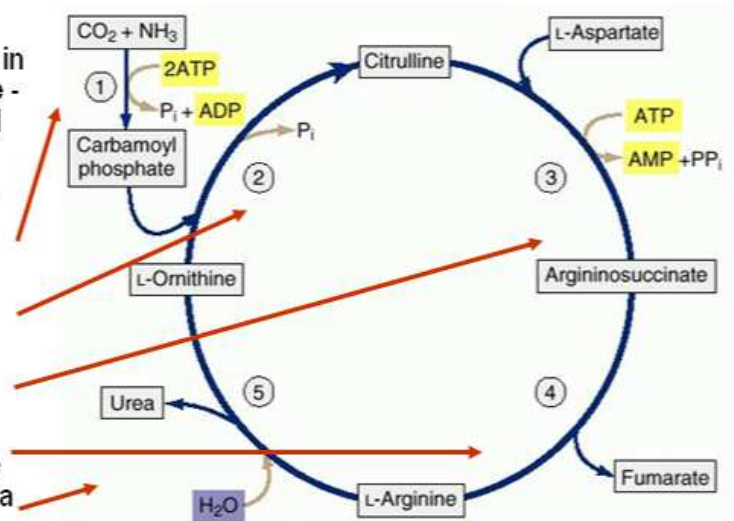
## Phenylketonuria



# Urea cycle defects

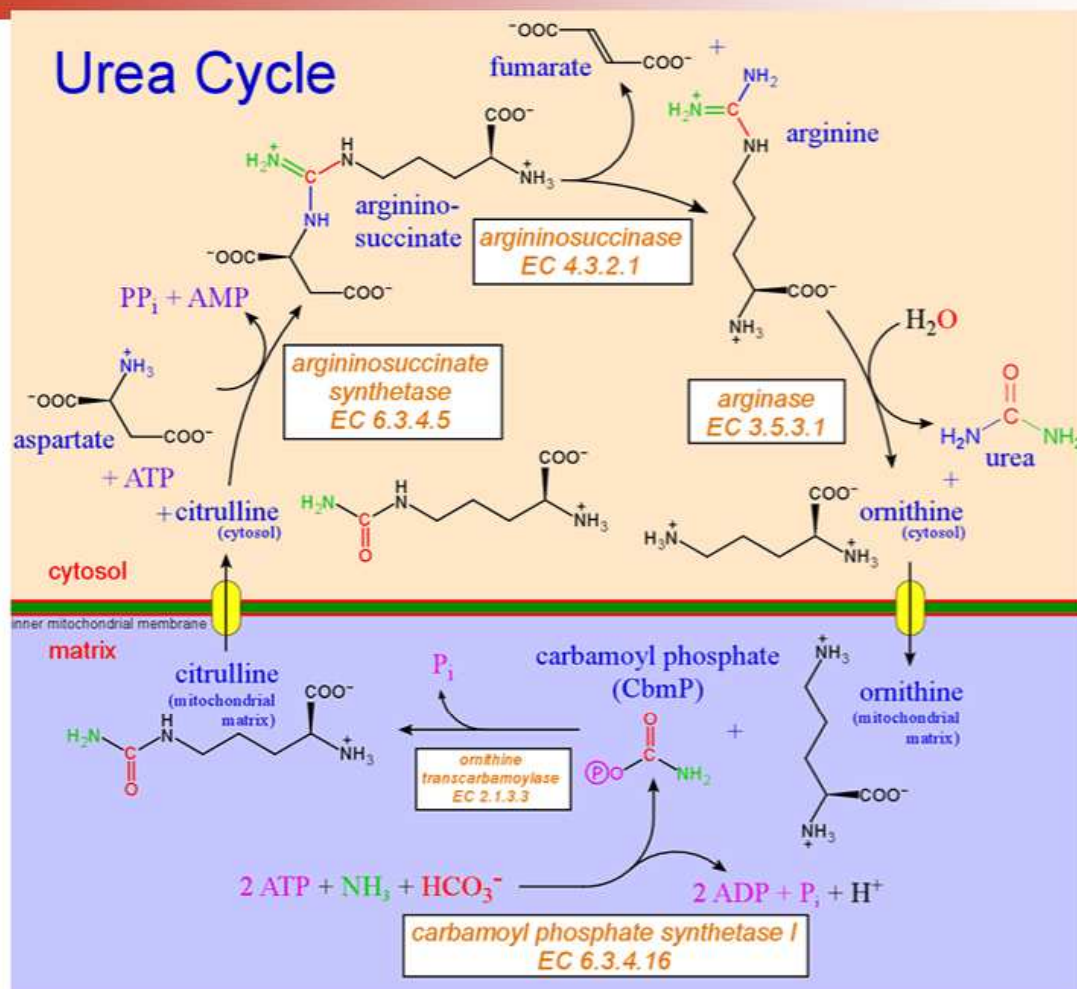
## Urea cycle defects

- **Ammonia** is a product of protein metabolism when it is elevated has a toxic effect on the CNS.
- In terrestrial vertebrates ammonia is converted to **urea** in the liver via the **urea cycle** and is excreted in the **urine** - the first metabolic pathway to be described by Krebs and Henseleit, in 1932
  - Carbamoyl phosphate is synthesized from  $\text{NH}_4 + \text{CO}_2, \text{H}_2\text{O}$ , and ATP by carbamoyl phosphate synthetase
  - L-Ornithine reacts with carbamoyl phosphate to give citrulline
  - Argininosuccinate synthetase catalyzes the condensation of citrulline and aspartate to argininosuccinate.
  - This is cleaved by argininosuccinase into arginine and fumarate. Arginase hydrates L-arginine to urea and L-Ornithine
- Mutations in genes encoding the enzymes of the urea cycle cause **5 hereditary disorders with high plasma levels of ammonium**
- The most common form is X-linked OTC resulting from **mutations in the OTC gene located at Xp21.1**. It has 10 exons spanning 73 kb of DNA.



- KEY TO ENZYMES (Circled Numbers)
1. Carbamoyl-phosphate synthase (ammonia)
  2. Ornithine carbamoyltransferase
  3. Argininosuccinate synthase
  4. Argininosuccinate lyase
  5. Arginase





## Urea cycle defects (UCD)

UCD	Enzyme Deficiency	Symptoms/Comments
1. Type I Hyperammonemia, CPSD	Carbamoylphosphate synthetase I	24h–72h after birth infant becomes lethargic, needs stimulation to feed, vomiting, hypothermia, hyperventilation, hyperammonemia; <b>T: arginine which activates <i>N</i>-acetylglutamate synthetase</b>
2. <i>N</i> -acetylglutamate synthetase deficiency	<i>N</i> -acetylglutamate synthetase	mild to severe hyperammonemia associated with deep coma, acidosis, recurrent diarrhea, ataxia, hypoglycemia, hyperornithinemia; <b>T: administration of carbamoyl glutamate to activate CPS I</b>
3. Type 2 Hyperammonemia, OTCD	Ornithine transcarbamoylase	most common, X-linked UCD, ammonia and amino acids elevated in serum, increased serum orotic acid <b>T: high carbohydrate, low protein diet, ammonia detoxification (sodium phenylacetate or sodium berzoate)</b>
4. Classic citrullinemia, ASD	Argininosuccinate synthetase	episodic hyperammonemia, vomiting, lethargy, ataxia, seizures, eventual coma: <b>T: arginine administration</b> to enhance citrulline excretion, <b>ammonia detoxification (sodium berzoate)</b>
5. Argininosuccinic aciduria, ALD	Argininosuccinate lyase	episodic symptoms similar to classic citrullinemia, elevated plasma and cerebral spinal fluid argininosuccinate: <b>T: diet with arginine and sodium berzoate</b>
6. Hyperargininemia, AD	Arginase	rare UCD, progressive spastic quadriplegia and mental retardation, ammonia + arginine high in cerebral spinal fluid and serum, arginine, lysine and ornithine high in urine: <b>T: diet of essential amino acids excluding arginine, low protein diet</b>

**Ammonia detoxification + low protein diet !!!**

# Symptoms of hyperammonemia

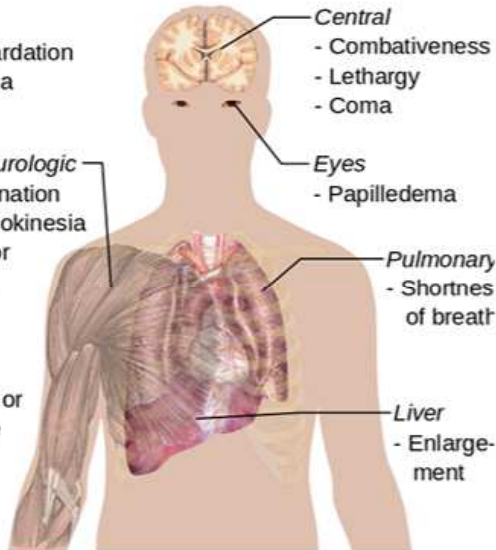
- vomiting, seizures, headache,
- mental status changes, (lethargy, coma)
- compensatory hyperventilation (fast breaths; compensates acidosis but may lead to respiratory alkalosis)
- muscle hypotonia/hypertonia, ataxia, tremor, seizures

**General**

- Growth retardation
- Hypothermia

**Muscular/Neurologic**

- Poor coordination
- Dysdiadochokinesia
- Hypotonia or hypertonia
- Ataxia
- Tremor
- Seizures
- Decorticate or decerebrate posturing



**Primary hyperammonemia** = caused by inborn errors + reduced activity of the enzymes in the urea cycle metabolism (UCD) = hyperammonemia + hypoglycemia with/out metabolic acidosis

**Secondary hyperammonemia** = inborn defect of enzymes that are not part of the urea cycle (e.g. propionic acidemia, methylmalonic acidemia) or dysfunction of cells that make major contributions to metabolism (e.g. hepatic failure).

- organic acidurias = hyperammonemia + anion gap metabolic acidosis

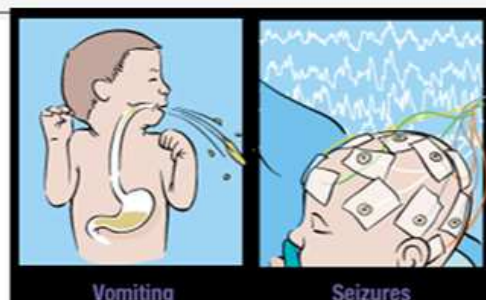
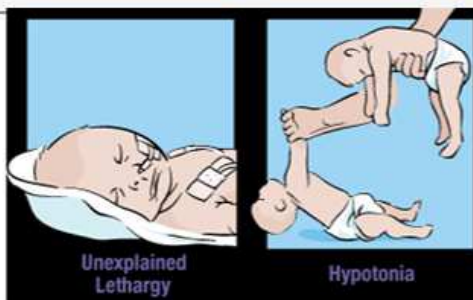
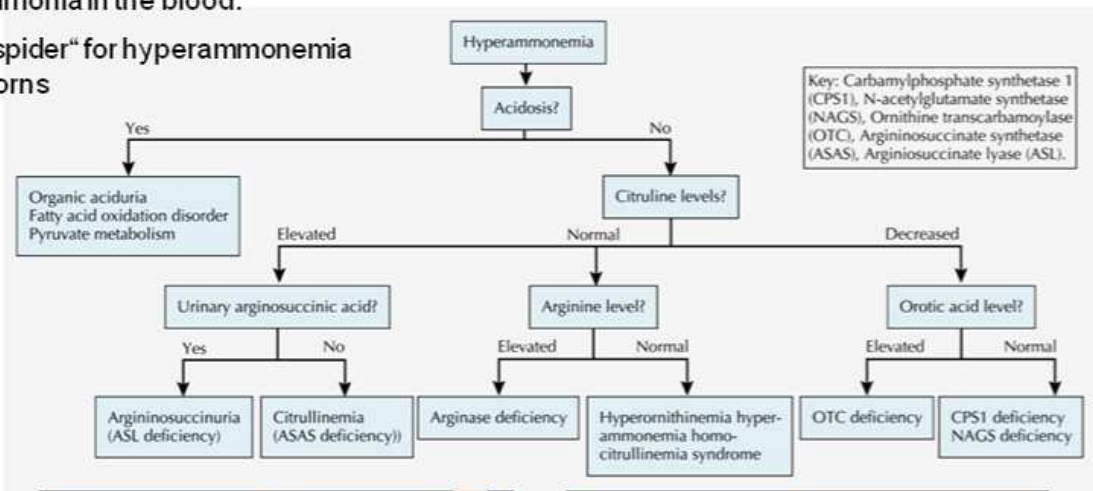
- fatty acid oxidation disorder (FAODs)
- hyperornithinemia-hyperammonemia-homocitrullinemia syndrome,
- pyruvate carboxylase deficiency,
- hyperammonemia-hyperinsulinemia syndrome.
- Sepsis; liver failure; medications: valproate; transient hyperammonemia of the newborn (resolves perinatally)

# Hyperammonemia

= is a metabolic disturbance characterised by an excess of ammonia in the blood.

It is a dangerous condition that may lead to encephalopathy and death.

Diagnostic "spider" for hyperammonemia in the newborns





# Metabolic disorders of hem

## Porphyrias

Group of enzyme deficiencies of haem synthesis leading to accumulation of various intermediates porphyrins affecting the skin, liver or nervous system: **a) inherited** (AD, AR, X-linked dominant, b) **acquired** (hemochromatosis,

### Erythropoietic porphyria:

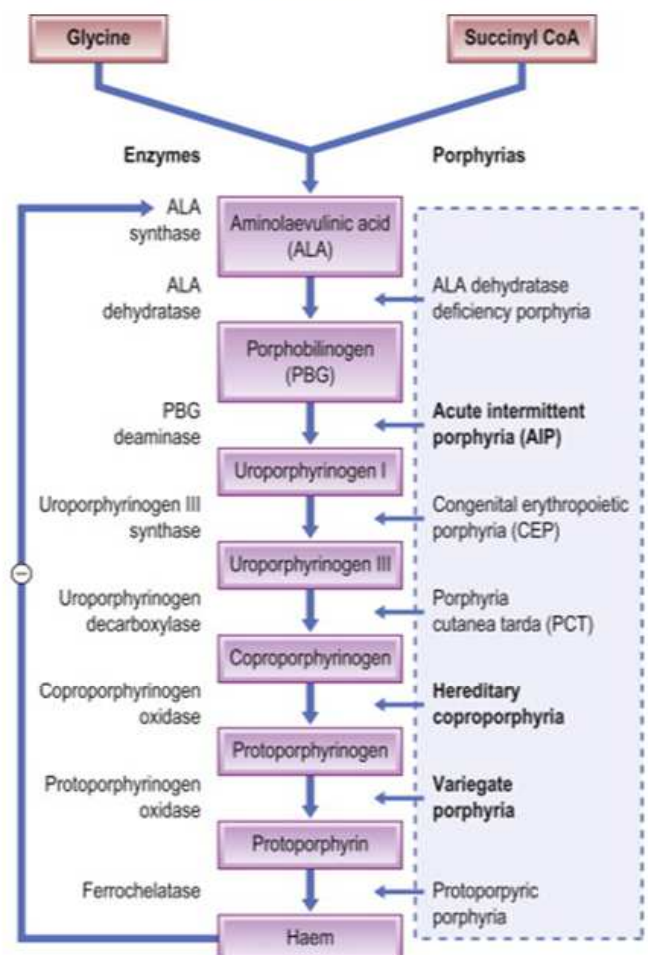
X-linked dominant protoporphyria (XLDPP),  
Congenital erythropoietic porphyria (CEP)  
Erythropoietic protoporphyria (EPP)

### Hepatic porphyria:

Aminolevulinic acid dehydratase deficiency porphyria (ALADP)  
Acute intermittent porphyria (AIP)  
Porphyria cutanea tarda (PCT)  
Hereditary coproporphyria (HCP) variegate porphyria (VP)

### Cutaneous porphyria

Congenital erythropoietic porphyria (CEP)  
X-linked dominant protoporphyria (XLDPP),  
Porphyria cutanea tarda (PCT)  
Erythropoietic protoporphyria (EPP)  
Hereditary coproporphyria (HCP)  
Variegate porphyria (VP)



# Acute porphyrias

- **Types:** acute intermittent porphyria (AIP), variegate porphyria (VP), aminolevulinic acid dehydratase deficiency porphyria (ALAD) and hereditary coproporphyria (HCP).
- **Clinic: predominantly neurological symptoms**
- attacks (days to weeks) triggered by alcohol, smoking, hormonal changes, fasting, stress, or certain medications; rapid in onset, last a short time
- affect CNS nervous system; episodic acute attacks; resolve once the attack passes
- Light forms: abdominal & chest pain, vomiting, confusion, constipation, fever, hypertension, tachycardia. skin is affected, blisters or itching may occur with sunlight exposure
- Severe forms: motor peripheral neuropathy, muscle weakness, quadriplegia; CNS: anxiety, confusion, hallucinations, seizures and coma. and, very rarely psychosis

# Cutaneous porphyria



Porphyria cutanea tarda

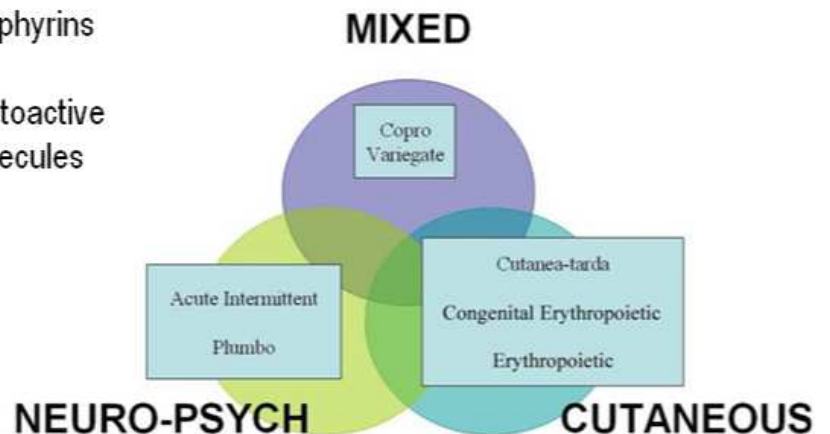


Acute intermittent porphyria



Change in urine color after sun exposure

Porphyrins are photoactive molecules





## Chronic porphyrias

- **Types:** X-linked dominant protoporphyria (XLDPP), congenital erythropoietic porphyria (CEP), porphyria cutanea tarda (PCT), and erythropoietic protoporphyria (EPP).
- **Clinic:** primary manifestation is in skin disease. **cutaneous porphyrias**; 2 distinct patterns
- **(A) Immediate photosensitivity:** (XLDPP, EPP.) 30 min after sun exposure : severe pain, burning, and discomfort in exposed areas (redness and swelling).
- **(B) Vesiculo-erosive skin disease** CEP, PCT, VP +HCP. blisters (vesicles)/open sores (erosions) noted in patients in sun-exposed areas (face, back of the hands).
- VP +HCP: Milder disease - skin fragility, blisters and erosions, particularly after minor knocks; heal slowly, small scars that may be lighter or darker than normal skin.
- PCT: More severe - darkening of exposed skin, hypertrichosis
- CEP, HEP most severe disease - hepatoerythropoietic porphyria (HEP); severe shortening of digits, loss of skin appendages such as hair and nails, severe scarring of the skin with progressive disappearance of ears, lips, and nose; deformed, discolored teeth or gum and eye abnormalities.

## Porphyrias



Hepatoerythropoietic porphyria (HEP)