Hereditary disorders of carbohydrate metabolism
Disorders of metabolism of monosaccharides („small molecules“)

Fructose

Galactose

Glucose

Disorders of metabolism of polysaccharides („large molecules“)

Glycogen storage disorders (also lack of product)

Disorders of glycosylation (proteins and lipids ...) product deficiency
Inherited disorders of fructose metabolism
Fructose

Fructose (β-D-fructofuranose)

Honey, vegetables and fruits

Disaccharide sucrose contains a fructose moiety

Sorbitol – sugar alcohol, derived from glucose, abundant in fruits. Sorbitol dehydrogenase converts sorbitol to fructose - a source of fructose.

GLUT5, GLUT-2 – glucose transporter isoforms responsible for fructose transport in the small intestine

Fructose is transported into liver cells mainly by GLUT-2
Inherited disorders of fructose metabolism

Daily intake of fructose in Western diets: 100 g

Metabolised in liver, kidney, intestine

Intravenous fructose in high-doses is toxic: hyperuricemia, hyperlactacidemia, ultrastructural changes in the liver.

Essential fructosuria

Hereditary fructose intolerance (aldolase B deficiency)

Hereditary fructose 1,6-bisphosphatase deficiency

Autosomal recessive disorders
Toxicity of fructose

Rapid accumulation of fructose -1-phosphate

The utilization of F-1-P is limited by triokinase

Depletion of ATP

Hyperuricemia
Hyperuricemic effect of fructose results from the degradation of adenine nucleotides (ATP).

Adenine dinucleotides → → → uric acid

Increase of lactate concentration
Hereditary fructose intolerance

Deficiency of fructoaldolase B of the liver, kidney cortex (isoenzymes A,B,C)

Severe hypoglycemia triggered by ingestion of fructose

Prolonged fructose intake: poor feeding, vomiting, hepatomegaly jaundice hemorrhage, proximal tubular renal syndrome, hepatic failure, death

Strong distaste for fructose-containing foods, may lead to psychiatric referrals

Fructose -1- phosphate inhibits gluconeogenesis (aldolase A), also glycogen phosphorylase

Patients are symptom-free on fructose-free diet

Diagnostics: (i.v. fructose tolerance test – abandoned), DNA analysis.
Hereditary fructose 1,6-bisphosphatase deficiency

Fructose 1,6-bisphosphatase catalyzes the irreversible splitting of fructose 1,6-bisphosphate into fructose 6-phosphate and inorganic phosphate (P).

Episodes of hyperventilation, apnea, hypoglycemia, ketosis and lactic acidosis, with potentially lethal course.

Episodes often triggered by fasting or infection, also by ingestion of larger amount of fructose. There may be chronic mild hyperlactacidemia.

Aversion to sweets does not develop, tolerance to fasting improves with age.

Autosomal recessive disorder.

Severe disorder of gluconeogenesis, gluconeogenetic precursors (amino-acids, lactate, ketones) accumulate after depletion glycogen in the patients.
Essential fructosuria

Deficiency of liver fructokinase

Asymptomatic metabolic anomaly - benign

Hyperfructosemia and hyperfructosuria – important for differential diagnosis of other fructose metabolism disorders
Hereditary disorders of glucose transport
Glucose transport

Hydrophillic glucose molecule does not cross easily lipohillic cellular membranes -> transporters are necessary to carry glucose across membranes

2 types of transporters:

a) Sodium-dependent glucose transporters (SGLTs, 'active' transporters encoded by SLC5 family members) – couple sugar transport to sodium electrochemical gradient -> can transport against concentration gradient

b) Facilitative glucose transporters (GLUTs, uniporter systems, 'passive' transporters) – transport glucose only along an existing gradient.
Glucose transport

**SGLT1 deficiency : Congenital Glucose/Galactose malabsorption**

*SGLT1* – sodium dependent transporter in the brush border of enterocytes

Promotes postprandial expression of GLUT2

Rare, autosomal recessive disorder, no polyhydramnion in pregnancy

**Profuse watery diarrhoea and bloating in the first days after birth**

Severe hypertonic dehydration, often with fever

Typically, gastrointestinal infection is suspected, with repeated failing attempts to switch patients from parenteral to oral feeds

Chronic dehydration may lead to nephrolithiasis and nephrocalcinosis in some cases

Acidic stool pH, reducing substances in stools, mild intermittent glucosuria. Glucose, galactose but not fructose provoke symptoms

**Treatment** : exclusion of glucose and galactose from the diet

Formula with fructose as the only saccharide
GLUT1 deficiency

GLUT1 (SLC2A1) – membrane glucose facilitating transporter
GLUT1 deficiency results in low CSF concentration (hypoglycorrhachia)

**Classic form:** early onset epileptic encephalopathy developing during the first year of life
Various types and frequency of seizures:
Often refractory to anticonvulsants, sometimes aggravated by fasting
Developmental delay, complex motor disease, in most severe cases microcephaly

**Non-classic form:**
Complex movement disorder without epilepsy: spastic-atactic gait, action limb dystonia, chorea, cerebellar action tremor, myoclonus
**Non-epileptic paroxysmal events** of ataxia, weakness, parkinsonism, alternating hemiplegia, nonkinesogenic dystonia

GLUT1 is expressed in erythrocytes: exercise-induced energy deficit may lead to haemolytic anemia
GLUT1 deficiency - continued

**Treatment:**
Ketone bodies are alternative fuel for the brain
Ketogenic', high-fat, low carbohydrate diets may restore brain energy metabolism (calories from fat/non-fat sources: 3/1 ... 4/1)
May control seizures and movement disorders, should be maintained throughout childhood into adolescence
Substances inhibiting GLUT1 should be avoided (anticonvulsants (phenobarbital, chlorohydrate, diazepam), methylxanthines (theophyllin, caffeine), alcohol and green tea.)

**Genetics:** both autosomal dominant and recessive inheritance described
About 80% of patients heterozygous for a GLUT1 mutation, most often de-novo

**Diagnostics:**
Low CSF glucose: < 2.5 mmol/l (normal > 3.3 mmol/l)
Low CSF-to-blood ratio (< 0.5)
Low glucose uptake in erythrocytes, low GLUT1 expression in erythrocytes
_Glut1_ mutation analysis
Suspicion for GLUT1 deficiency

• any form of intractable epilepsy, in particular early onset absence epilepsy;

• global developmental delay, particularly in speech;

• complex movement disorders;

• paroxysmal events triggered by exercise, exertion, or fasting.

http://www.g1dfoundation.org/youtube/
Hereditary disorders of galactose metabolism
Hereditary disorders of galactose metabolism

The main sources of galactose are milk and milk products.

Galactose is present as the disaccharide lactose (β-D-galactopyranosyl-(1→4)-D-glucose)

**Genetic disorders:**
Galactokinase

Galactose-1-phosphate uridyltransferase

Uridine diphosphate galactose 4-epimerase.
Classical galactosemia: galactose-1-phosphate uridyltransferase deficiency

In the first weeks of life: **poor feeding and weight loss, vomiting, diarrhea, lethargy, and hypotonia.**

**Severe liver dysfunction, hepatomegaly,** icterus (often conjugated hyperbilirubinemia), bleeding diathesis, septicemia, renal tubular syndrome.

**Cataracts**: osmotic oedema of the lens due to galactitol

Elevated galactose, galactitol, galactose-1-phosphate

**Late complications**
- Cognitive defects
- Ovarian failure in females
- Ataxia, low bone density.

AR, incidence 1:40 000- 60 000,
**Neonatal screening** for galactose in some countries

Variants (Duarte)
Galactitol formation by nonspecific aldose reductase

Fig. 72-3 The conversion of galactose to galactitol by a nonspecific aldose reductase and to galactonic acid by aldehyde dehydrogenase.
Cataracts in classical galactosemia

Galactitol – osmotic swelling of lens fibres
Galactokinase deficiency

Cataracts - usually bilateral and detectable in the early weeks of life

Pseudotumor cerebri

Galactitol – osmotic oedema of lens

Treatable by galactose-restricted diet, cataract can resolve

Autosomal recessive, rare condition (cca 1:200 000)
Uridine diphosphate galactose 4-epimerase deficiency

**Severe form:**

Severe deficiency of epimerase activity
Extremely rare

Newborns with vomiting, hepatopathy resembling classical galactosemia.
Mental retardation

**Mild form:**

Partial deficiency of epimerase deficiency
In most patients apparently benign condition

**Intermediate forms**

Autosomal recessive
Hereditary disorders of glycogen metabolism
Glycogenoses
Glycogen storage disorders

Glucose: primary source of energy for eukaryotic cells

Glycogen: macromolecular storage form of glucose – branched chain polysaccharide composed of glucose units. Synthesis of glycogen starts at protein „primer“ - glycogenin

Straight chains α-1,4 linkages branch points α-1,6 linkages at intervals of 4-10 glucose residues

Only glucose from liver glycogen is released into circulation.

In the muscle: glycogen β particles- up to 60 000 glucose residues, up to 2% of wet weight,
In the liver: α particles „aggregates“ β particles, glycosomes, up to 8% of wet weight, glycogenin 2

Glycogenoses: hereditary enzymopathies that result in storage of abnormal amounts and/or forms of glycogen
Glycogen storage diseases - overview

Hepatic glycogenoses – present principally with *hypoglycemia, ketosis, hyperlactacidemia, stunted growth* (GSD I, GSD III, GSD 0) or mainly with *hepatomegaly* with hepatopathy (GSD VI, GSD IV, GSD IX)

Muscle glycogenoses – present with *exercise intolerance, cramps after exercise, rhabdomyolysis* (GSD V, GSD VII and some very rare deficiencies)

Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy
GSD II - deficiency of lysosomal alpha glucosidase, presents with myopathy and cardiomyopathy

(deficiency of LAMP 2 – disorder of autophagy – see lecture on lysosomal diseases)
AMP-activated protein kinase deficiency – presents with adult cardiomyopathy and Wolf-Parkinson-White syndrome

Brain glycogenoses – present with adult neurodegeneration, epilepsy and accumulation of polyglucosan bodies. also Lafora disease
Glycogen metabolism and glycogen storage disorders

Roman numerals indicate GSD type
Red: liver glycogenoses
Violet: muscle glycogenoses
Green: generalized glycogenosis
* associated with hypoglycemia

Modified from O Lathrev et al, in Saudubry et al (eds) Inborn Metabolic Diseases
Liver glycogenoses
*Fasting hypoglycemia, hepatomegaly, growth retardation*
5 types - most common is type I (von Gierke disease- glucose-6-phosphatase deficiency)
or hepatomegaly without tendency to hypoglycemia

Muscle glycogenoses
*Intolerance of exercise, cramps induced by exercise, rhabomyolysis, the heart is not affected*
6 types

Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy
Type II (Pompe disease) Lysosomal α-1,4-glucosidase
- lysosomal storage of normal glycogen
- activated AMP protein kinase deficiency: W-P-W syndrome

Brain glycogenoses
Adult polyglucosan body disease, Lafora disease and other disorders neurodegenerative disease with adult onset, epilepsy,
- accumulation of polyglucosan bodies
Liver glycogenoses

*Fasting hypoglycemia, hepatomegaly, growth retardation or hepatomegaly without tendency to hypoglycemia*

prototypical GSD: GSD I? von Gierke disease- glucose-6-phosphatase deficiency), incidence approx. 1:100 000
common: GSD IX: phosphorylase kinase deficiency : incidence approx. 1:100 000
Type I Glycogen Storage Disease (Glucose 6-Phosphatase Deficiency, von Gierke Disease)

Excessive accumulation of glycogen in liver, kidney and intestinal mucosa

Patients usually present in infancy with hepatomegaly and/or hypoglycaemic seizures, hyperlactacidemia after a short fast, episodes of hyperpnoe and irritability

Gout, hyperlipidemia (hypertriglyceridemia), skin xanthomas

Doll-like face, thin extremities, short stature, protuberant abdomen (hepatomegaly), inflammatory bowel disease

Later in life progressive fibrosis, liver adenomas - cave: malignant transformation. Atherosclerosis

Fasting tolerance improves with age, late complications

Treatment goal: maintaining normoglycemia, frequent feeding, nocturnal nasogastric drips in infancy, uncooked cornstarch, liver transplantation, kidney transplantation

Autosomal recessive, overall incidence is 1:10000, frequent in Ashkenazi

The diagnosis is based on clinical presentation, abnormal blood/plasma concentrations of glucose, lactate, uric acid, triglycerides, and lipids, and molecular genetic testing.
Glucose -6-phosphatase system

Localized to *luminal* face of ER

Type Ia GSD: deficient activity of phosphatase
Type Ib GSD: a defect in the microsomal membrane transport system of G-6-P

Non-a type associated with *neutropenia and inflammatory bowel disease* with recurrent bacterial infections and oral ulcers
The metabolic consequences of GSD I
Type III Glycogen Storage Disease (Debrancher Deficiency; Limit Dextrinosis; Cori or Forbes Disease)

Both liver and muscle are affected: frequent cirrhosis, myopathy, often cardiomyopathy, with fasting ketotic hypoglycemia about 15% percent of patients have only hepatic presentation myopathic presentation - also in adulthood Abnormal glycogen: limit dextrin

Type IV (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)
Abnormal glycogen resembling amylopectin – fewer branching points presents in infancy with progressive liver failure leading to cirrhosis, rare hypoglycemias, cardiomyopathy death at 4-5 years without liver transplantation

Neuromuscular presentation - accumulation of polyglucosan bodies in tissues - myopathy, arthogypassis

adult polyglucosan body disease
Type IX Glycogen Storage Disease (deficiency of phosphorylase kinase (PhK) and subunits)

Degradation of glycogen is regulated by a metabolic cascade resulting in activation of glycogen phosphorylase by phosphorylase kinase.

Phosphorylase kinase enzyme has four copies of 4 subunits each - α, β, γ, δ. Subunit γ is catalytic, subunits α and β are regulatory, δ is calmodulin.

The most common form (90% of cases), liver PhK deficiency (X-linked liver glycogenosis) is due to the deficiency of liver form of α subunit.

deficiency of muscle form of α subunit: X-linked muscle glycogenosis
deficiency of subunit β: autosomal recessive PhK deficiency in liver and muscle;
deficiency of subunit γ, autosomal recessive liver PhK deficiency.
Activating mutations in PRKAG2, gene encoding γ subunit of AMP-activated Protein Kinase (AMPK), lead to glycogen accumulation in cardiac muscle and supraventricular arrhythmias

Activated AMPK increases glucose influx into cells

AMPK is a cellular energy sensor. It is activated by exercise in muscle and an increase in the AMP/ATP ratio. Heterotrimeric complex: a catalytic subunit (α) and two regulatory γ.

Mutations in the gene encoding γ subunit (PRKAG2) cause ventricular pre-excitation (Wolf-Parkinson-White syndrome) predisposing to supraventricular arrhythmias. Fully penetrant autosomal dominant trait.

Other phenotypic features:
Hypertrophic cardiomyopathy

Mutant AMPK permanently stimulates glucose influx into cell, resulting elevation of G6P activates glycogen synthase.

Arrow: typical delta wave of W-P-W syndrome
Brain glycogenoses

Adult polyglucosan body disease

Deficiency of the branching enzyme in astrocytes (GSD IV)
Slowly progressive gait disturbance, urinary incontinence,
loss of sensitivity in lower extremities, later cognitive decline

In peripheral nerves and in the brain storage of amylopectin-like glycogen in polyglucosan bodies

Rare, found almost exclusively in Ashkenazi Jewish patients, AR

Lafora disease

Progressive severe myoclonic epilepsy with onset usually in adolescence, progressive dementia, aphasia, apraxia
Leads to vegetative state and death in 10 years from onset

Lafora bodies in neurons - abnormal glycogen storage

Mutations in laforin carbohydrate-binding phosphatase and the malin E3 ubiquitin ligase
Enzyme deficiency is not known
Muscle glycogenoses (without cardiac involvement)

Exercise intolerance, often followed by rhabdomyolysis

Prototypical disease: GSD V, McArdle disease, deficiency of myophosphorylase
Myalgia and stiffness of exercising muscles relieved by rest, often rhabdomyolysis, later in life may be present muscle wasting

AR inheritance

No pharmacological treatment

(Dif.dg. of post-exercise rhabdomyolysis: CPT II or lipin1 deficiency)
Generalized glycogenosis: Morbus Pompe
M. Pompe

Deficiency of lysosomal acid alpha-glucosidase (acid maltase)
Lysosomal storage of glycogen with normal structure

**Infantile type:**
First symptoms in the first months of life: cardiomegaly, muscle weakness, macroglossia
Progressive course, death due to cardiopulmonary failure in the first two years of life

**Adult type**
Slowly progressive proximal myopathy and/or slowly progressive respiratory failure
Heart is not affected

**Intermediate types**
Myopathy, heart can be affected

**Diagnostics:**
Glycogen storage in tissues
measurement of enzyme activity
Mutation analysis
Treatment monitoring: glucose tetrasaccharide Glc4

**Treatment**
Enzyme supplementation therapy (Myozyme)
Congenital disorders of glycosylation (CDG)
Hereditary disorders of glycosylation

Disorders of protein glycosylation

N-glycosylation, O-glycosylation, ...

Disorders of lipid glycosylation

Disorders of dolichol synthesis

Disorders glycoprophosphatidylinositol synthesis

Combined defects

Subcellular compartments:
ER, Golgi, cytosol

Overall more than 100 disorders
Glycoproteins

N-glycosylation

O-glycosylation

Disorders of glycosylation:
CDGs (previously known as carbohydrate-deficient glycoprotein syndromes)
Most Proteins Synthesized in the Rough ER Are Glycosylated by the Addition of a Common N-linked Oligosaccharide

Precursor oligosaccharide is bound to dolichol in the ER membrane

Oligosaccharides are further processed in ER and Golgi
Man₅GlcNac₂

Glc₃Man₉GlcNac₂
Processing of oligosaccharide chains of glycoproteins in ER and Golgi
O-glycosylation

Saccharide units are bound to Thr or Ser hydroxyl

Threonin
Serin

7 groups (classification after the first saccharide)

Glycosyltransferases add other saccharide unit in the Golgi apparatus
Congenital disorders of N-glycosylation

CGD I: >16 disorders of N-glycan assembly (CDG Ia-m) including dolichol-phosphate synthesis defects

(CDG Ia: phosphomannomutase 2 deficiency)

CDGII: >8 disorders of processing of N-glycans

Congenital disorders of O-glycosylation
> 6 disorders

Disorders of glycolipid glycosylation
3 disorders: GM3 synthase deficiency, ...

Highly variable phenotype
Autosomal recessive disorders
Autosomal dominant : 1 disorder (hereditary multiple exostoses sy.)
Congenital disorders of glycosylation

Aberrant protein glycosylation

Diagnostic paradigm:
analysis of glycans → molecular defect

Screening:
Isoelectric focusing of **sialyltransferin** in defects of N-linked glycans
Isoelectric focusing of **apo CIII** in defects of N-linked glycans

Structural analysis of glycans

Measurement of enzyme activities

Mutation analysis

**CDG-x:** abnormal glycosylation detected by screening techniques, but with unknown molecular defect
Isoelectrofocusing of serum sialotransferins

A, G controls,
B to F: **type-I pattern**
B phosphomannomutase def., C phosphomannose isomerase (PMI) deficiency D, hypoglucosylation defect; E, F unidentified
H to J: **type-II pattern**
H, N-acetylglucosaminyltransferase (GnT II) def; I, Junidenti®ed
Glycoproteins Reported to Be Abnormal in Phosphomannomutase Deficiency and Showing an Abnormal Pattern on Isoelectrofocusing, Two-dimensional Electrophoresis, Western Blotting, and/or Decreased or Increased Concentration or Enzymatic Activity

**Serum**
Transport Proteins
Apooprotein B, apoprotein CII, apoprotein E, ceruloplasmin-haptoglobin, α2-macroglobulin, retinol-binding protein, sex hormone-binding globulin, thyroxine-binding globulin, transcobalamin II, transcortin, transferrin, vitamin D-binding globulin

Coagulation and Anticoagulation Factors
Antithrombin, α2-antiplasmin, coagulation factors II, V, VI, VIII, IX, X, XI, and XII, heparin cofactor II, plasminogen, protein C, protein S

Hormones
Follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone

Lysosomal Enzymes
Arylsulphatase A, α-fucosidase, β-glucuronidase, β-hexosaminidase

Other Enzymes
N-Acetylglucosaminidase, carboxypeptidase

Other Glycoproteins
Amyloid P, α1-acid glycoprotein, α1-antichymotrypsin, α1-antitrypsin, α1-B glycoprotein, clusterin, complement C3a, complement C4a, complement C1 esterase inhibitor, α2-HS glycoprotein, immunoglobulin G, orosomucoid, peptide PLS:29, peptide PLS:34, Zn-a2-glycoprotein

Cerebrospinal Fluid
β-Trace protein, transferrin

Leukocytes
Lysosomal Enzymes
α-Fucosidase, β-glucuronidase, α-iduronidase, α-mannosidase, β-mannosidase

Sialoglycoproteins on B lymphocytes

Fibroblasts
Biglycan, decorin

Liver
α1-Acid glycoprotein, α1-antitrypsin, haptoglobin, transferrin

Glycosylation defects lead to abnormal glycoproteins, which normally have diverse functions
Grünewald 2007
Patients with CDGs can be referred to specialists in different fields of medicine.
Symptoms of CDGs due to defects of N-linked glycans

CDG-Ia.
In infancy: Inverted nipples, abnormal subcutaneous fat distribution, and cerebellar hypoplasia, facial dysmorphism, hypotonia, and psychomotor retardation. Alternating strabism and other eye movement disorders, skeletal abnormalities.
After infancy: Stroke-like episodes, pigment retinitis, ataxia, peripheral neuropathy

Clinical course:
infantile multisystem stage, late-infantile and childhood ataxia-mental retardation stage, and adult stable disability stage.

CDG-Ib. Phosphomannoisomerase deficiency
Cyclic vomiting, profound hypoglycemia, failure to thrive, liver fibrosis, and protein-losing enteropathy, occasionally coagulation disturbances without neurologic involvement,

Treatment: mannose 50-1g/kg/day

CDG-Ic.
Mild to moderate neurologic involvement with hypotonia, poor head control, developmental delay, ataxia, strabismus, and seizures, ranging from febrile convulsions to epilepsy
The clinical presentation is milder than in CDG-Ia;
Recognizable clinical features in different N-linked glycosylation defects. a Abnormal fat distribution in phosphomannomutase 2 (PMM2)-CDG (CDG-Ia). b Liver cirrhosis in phosphomannose isomerase (MPI)-CDG (CDG-Ib). c Distal phalangeal aplasia in ALG6-CDG (CDG-Ic). d Ichthyosis and iridial and retinal coloboma are characteristic for SRD5A3-CDG. e Distal arthrogryposis in ALG8-CDG (CDG-Ih). f Myasthenic face and ptosis are common in DPAGT1-CDG (CDG-Ij). g Venous thrombosis leads to asymmetry in limb circumference in ALG1-CDG (CDG-Ik). Scott K et.al. JIMD 2014, Volume 37, Issue 4, pp 609–617
Treatment of phosphomannose isomerase deficiency by mannose supplementation
Selected O-glycosylation disorders

**Multiple hereditary exostoses**
Autosomal dominant
Incidence 1/50 000
**Osteochondromas** of long bones
Compression of peripheral nerves and blood vessels
Limited joint movements
Increased probability of malignant transformation

Mutations in exostosin 1 and exostosin 2 genes

**Walker-Warburgův syndrom**
A neuronal migration disorder
Lissencephaly, corpus callosum agenesis, cerebellar agenesis
Brain and eye dysgenesis
Muscular dystrophy
Testicular dysgenesis in males
Death often before 1 year of age
A defect in glycosylation of **α-dystroglycan**
O-manosyltransferase I deficiency