Disorders of Carbohydrates Metabolism

- Disorders of Galactose Metabolism
- Glycogen Storage Diseases
- Diabetes Mellitus
Disorders of Galactose Metabolism
GALACTOSE

- Galactose is a sugar that is found mainly in milk.
- When lactose is broken down in the body, glucose and galactose are produced.
- Galactose is converted into glucose in the body for energy in the Leloir pathway.
GALACTOSE METABOLISM

Galactose is converted to galactose-1-phosphate by galactokinase (GALK). ATP and ADP are involved in this reaction. Galactose-1-phosphate is then used to produce UDP-glucose and UDP-galactose by UDP-galactose 4′-epimerase (GALE). Glucose-1-phosphate is also produced in this process. Excess accumulation leads to galactonic acid and galactitol.
GALACTOSE METABOLISM

- Galactose is taken up by cells and then converted to glucose via a 3 enzyme pathway known as the Leloir Pathway
- **STEPS:**
  1. α-D-galactose is phosphorylated to galactose 1-phosphate by galactokinase (GALK)
  2. A UMP group is transferred from UDP-glucose to galactose 1-phosphate, generating glucose 1-phosphate and UDP-galactose by galactose-1-phosphate uridyltransferase (GALT)
  - glucose 1-phosphate proceeds into glycolysis
  3. UDP-galactose is converted to UDP-glucose by UDP-galactose 4-epimerase (GALE) to complete the pathway
- **Galactosemia** occurs when mutations lead to a deficiency in any one of these enzymes
The conversion of galactose to galactitol by aldose reductase and to galactonic acid by aldehyde dehydrogenase.
TYPE I: CLASSIC GALACTOSEMIA

- The most common form (95%)
- Most severe form
- **Autosomal recessive disorder**
- Mutations in the GALT gene located on short arm of chromosome 9
- Codes for the enzyme *galactose-1-phosphate uridyltransferase*
- Most of these mutations severely diminish or eliminate the activity of the enzyme causing galactosemia
- Accumulation of *galactose 1-phosphate* becomes toxic and causes many severe complications
Incidence:
Type 1: 1/30,000 to 1/60,000 for classic galactosemia

Age:
Neonatal onset, some complications evident later on in life
TYPE I: CLASSIC GALACTOSEMIA

Genetic

- More than 190 mutations in the GALT gene have been identified
- Glutamine replaced with Arginine (Q188R)
  - most common mutation
  - most common in Caucasians
- Serine replaced with Leucine (S135L)
  - most common in people of African Descent
- Duarte variant: Asparagine replaced with Aspartic acid (N314D)
  - 5% of general population
  - Reduces enzymatic activity by 50%
  - Milder symptoms
Biochemical Findings

• Galactosemia and galactosuria.
• Hyperaminoaciduria and hyperalbuminuria. (owing to the early development of a proximal renal tubular)
• Accumulation of gal-1-ph, galactitol and galactonate in tissues.
• Increased serum bilirubin.
• Decreased hemoglobin.
• Accumulation of Gal-1-ph in tissues is the main cause of symptoms.
• Conversion of galactose in eye into galactitol cause early cataract. (the eye lens is imperiable to galactitol, so excess galactitol increases the osmotic pressure inside the lense leading to excessive hydration→ cataract)
SIGNS AND SYMPTOMS

- At birth: Jaundice after milk consumption
- Feeding difficulties
- Vomiting and diarrhea
- Aminoaciduria: High levels of amino acids in urine and/or plasma
- Hepatomegaly
- Hypoglycemia
- Ascites - fluid accumulation in the abdomen
- High Galactose concentrations in blood and urine
• Individuals with a profound deficiency of GALT can phosphorylate ingested galactose but fail to metabolize galactos 1-phosphate.

• As a consequence, galactose-1-phosphate and galactose accumulate, and the alternate pathway metabolites, galactitol and galactonate, are formed.

• Cataract formation can be explained by galactitol accumulation.

• The pathogenesis of the hepatic, renal and cerebral disturbances is related to the accumulation of galactose-1-phosphate and (perhaps) of galactitol.
Clinical Findings in Galactosemic Patients

Infants

- Poor Weight Gain
- Feeding Difficulties
- Jaundice
- Vomiting
- Diarrhea
- Lethargy
- Hypotonia
- Hepatomegaly
- Sepsis
- Hemolytic anemia

- If untreated → cataract, mental retardation, kidney dysfunction, liver cirrhoses and death in many infants because of infection and hepatic failure.

*Symptoms appear in the second half of the first week and include refusal to feed, vomiting, jaundice and lethargy.
*Hepatomegaly, edema and ascites may follow.
*Death from sepsis may follow within days but it has been noted as early as 3 days of age.
*cataracts appear within days or weeks
DIAGNOSIS

• By the presence of galactose in urine and blood with normal or low blood sugar while the infant is being fed breast milk or a formula containing lactose.
• A simple urine test (Benedict test) indicates the presence of a reducing substances.
• Measurement of enzyme activity in the red blood cells (fluorometric assay and Beutler assay)
• Prenatal diagnosis by direct measurement of the enzyme galactose-1-phosphate uridyl transferase in cultured amniotic cells.
TREATMENT

- **Removal** of galactose from diet. Avoid milk products and anything containing lactose or galactose. For infants, milk can be substituted with lactose-free formula or soya formula.
- Calcium and vitamin supplements are recommended.
- Pregnant women at risk should restrict intake of galactose to protect an affected fetus.
- **Neonatal screening** for diagnosis and treatment of classical galactosemia, is very important to prevent life threatening complications.
The gene locus of the enzyme is polymorphic, i.e., a high number of alleles can occupy the same locus. Over 200 GALT gene mutations have been detected!
### Galactose-1-phosphate uridyltransferase variants

<table>
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<tr>
<th>Variant forms (Ref)</th>
<th>RBC, Activity (% of Normal)</th>
<th>Mobility on Starch Gel</th>
<th>Neonatal signs</th>
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<sup>a</sup>10 percent activity in liver and intestine.

<sup>b</sup>Enzyme inactivated by product of GALT reaction (Glc-1-P).
TYPE II: GALACTOKINASE DEFICIENCY

- Autosomal recessive disorder. Incidence about 1:100,000 to 1:250,000.
- Galactokinase gene on chr 17
- Over 20 different mutations have been identified
- The only and main clinical finding is early cataract.
- Biochemical findings are galactosemia (about 100mg/dl), galactosuria, excretion of large amounts of galactitol & galactonic acid
- Diagnosis is confirmed by enzyme assay in RBCs.
- Prenatal diagnosis by enzyme assay in cultured amniotic cells
- Treatment by removal galactose from diet
- Pregnant women at risk should restrict intake of galactose to protect an affected fetus
TYPE III: GALACTOSE EPIMERASE DEFICIENCY

- **Gene:** UDP-galactose-4-epimerase (GALE) on chromosome 1
- **Enzyme:** UDP-galactose-4-epimerase
TYPE III: GALACTOSE EPIMERASE DEFICIENCY

- The rarest of the three forms of galactosemia
- Two forms; severe and benign.
- Both forms are autosomal recessive.

Increased gal-1-p in RBCs and a small increase in blood glucose.
The decrease in enzyme activity in benign form is confined to the RBCs & WBCs but normal in liver.
TYPE III: GALACTOSE EPIMERASE DEFICIENCY

Generalized Form (Severe)
- reduces the activity of the enzyme throughout the cells of the body
- Complications: cataracts, intellectual disability, liver damage, kidney damage, brain damage

Peripheral Form (Benign)
- reduces the activity of the enzyme in red blood cells only
- Complications: often will not see any of the complications that commonly occur in galactosemia