Errors in the metabolic pathways can lead to a number of diseases. Glycogen storage disease is a common carbohydrate metabolism disorder. There are 7 types of GSD, of which type I, II and V are more common. Galactosemia results from GALT deficiency. Symptoms are seen once milk is introduced. Phenylketonuria is the most common error of amino acid metabolism. Other amino acid disorders include homocystinuria, alkaptonuria and organic academia.

Definition of Errors of Metabolism

Inborn errors of metabolism are rare genetic diseases that arise from enzyme or transport protein defect and result in a blockade of the metabolic pathways.

Manifestations of these diseases arise from:

- Toxic accumulation of substrates
- Toxic accumulation of intermediates from other pathways
- Deficiency of products
- Combination of the above three

### Epidemiology of Errors of Metabolism

In general, the diseases present in 1 of 800 live births. Phenylketonuria is the most common disorder of amino acid metabolism. It is one of the commonest inborn errors of metabolism, representing an incidence of 1 in 15,000.

The diseases present mostly in infancy, but they are also evident in adulthood.

### Metabolic Pathways

- Pentose phosphate shunt
- Urea cycle
- Krebs cycle

Any defect in the bottom two pathways can lead to problems related to glycogen storage, amino acid metabolism, and fatty acid metabolism.

### Disorders of Carbohydrate Metabolism

**Problems of carbohydrate metabolism involve:**

- Glucose
- Fructose
- Galactose

**Glycogen storage diseases (GSD)**

Enzyme defects in glycogen degradation result in an inability to synthesize glucose in the liver and muscles during short periods of fasting. This leads to the accumulation of high amounts of glycogen in the liver. Meanwhile, the patient suffers from hypoglycemia.

**There are 7 types of GSD:**
- GSD I (von Gierke disease): Lack of the enzyme Glucose-6-Phosphatase
- GSD (Pompe’s disease): Deficiency of the enzyme alpha-1,4-glucosidase
- GSD III (Cori disease): Deficiency of a debrancher enzyme
- GSD IV (amylopectinosis): Deficiency of a branching enzyme
- GSD V (McArdle disease): Deficiency of muscle phosphorylase
- GSD VI (Hers disease): Hepatic phosphorylase deficiency
- GSD VII (Tarui disease): phosphofructokinase deficiency

Von Gierke’s GSD I

**Signs and symptoms:**

- Hypoglycemia (pallor, cyanosis, apnea, and loss of consciousness)
- Convulsions
- Hepatomegaly leading to abdominal distension
- Hyperlipidemia
- Kidney enlargement
- Fat deposits on the face resulting in round cheeks.
- Normal mental development
- Growth failure
- Delayed onset of puberty
- Pseudocolitis resulting in diarrhea
- Renal stones
- Hypertension
- Deterioration of renal functions
- Changes in the skin and mucous membrane
- Xanthomas on extremities
- Gout
- Aphthous ulcers

Pompe’s GSD II

**Signs and symptoms:**

**Infantile form:**

- Gout
- Aphthous ulcers
- Hypotonia
- Rapidly progressing muscle weakness
- Respiratory and feeding difficulties
- Scarce spontaneous movements
- Weak motor reactions to painful stimulus
- Mental functions are normal
- Tongue fasciculations
- Cardiomyopathy
- Heart failure

**Juvenile form:**

- Retarded motor development
- Hypotonia
- Respiratory insufficiency
- Muscle weakness
- Atony of the anal sphincter, in minority
- Cardiomyopathy – absent
- Macroglossia – absent

**Adult form:**

- Diminished tendon reflexes
- Intracranial aneurysm
- Decreased muscle volume

**McArdle’s GSD V**

**Signs and symptoms:**

- Fatigue on physical exertion
- Muscle weakness
- Muscle cramps
- Respiratory insufficiency
- Renal problems from myoglobin
- Burgundy red urine

**Diagnosis:**

<table>
<thead>
<tr>
<th>GSD type I</th>
<th>GSD type II</th>
<th>GSD type V</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serum glucose</td>
<td>• Creatine kinase (CK) levels (elevated)</td>
<td>• Serum CK at rest (elevated) after intensive exercise</td>
</tr>
<tr>
<td>• Electrolyte levels</td>
<td>• Serum aspartate aminotransferase levels (elevated in infants)</td>
<td>• CK levels further increase on exercise</td>
</tr>
<tr>
<td>• Serum lactate level</td>
<td>• Acid alpha-1,4-glucosidase activity measurement</td>
<td>• Blood ammonia, hypoxanthine, and inosine levels are high</td>
</tr>
<tr>
<td>• Serum triglycerides</td>
<td>• Enzymatic assay</td>
<td>• Uric acid concentrations (high)</td>
</tr>
<tr>
<td>• Serum cholesterol levels</td>
<td>• Molecular analysis for prenatal diagnosis</td>
<td>• Muscle phosphorylase activity (extremely low)</td>
</tr>
<tr>
<td>• Gamma-glutamyl transferase level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Complete blood count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Blood pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum uric acid level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Urinalysis in older patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Uric acid and calcium excretory levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum alkaline phosphatase, phosphorus, calcium, and urea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum creatinine levels</td>
<td></td>
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</tr>
</tbody>
</table>

**Treatment:**

<table>
<thead>
<tr>
<th>GSD type I</th>
<th>GSD type II</th>
<th>GSD type V</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptomatic therapy</td>
<td>• IV infusion of recombinant DNA glucosidase alfa (Myozyme).</td>
<td>• There is no specific treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal insufficiency may require hospital administrations.</td>
</tr>
</tbody>
</table>

**Galactosemia**

Galactosemia is an autosomal recessive inborn error of carbohydrate metabolism that results in the inability of the body to metabolize galactose into glucose.
Causes

Galactosemia is an inherited disorder. If both parents are affected, each child has a 25% chance of inheriting the disease.

Types

There are three forms of Galactosemia:

1. **Classic galactosemia/ type I galactosemia**
   
   This is the most common and most severe form that arises from deficiency of Galactose-1 phosphate uridyl transferase. The disease presents days after birth with lethargy, failure to thrive, jaundice and other features of liver injury.

2. **Type II galactosemia**
   
   This variety results from deficiency of galactose kinase. It is a mild variety with very few, if any, clinical manifestations.

3. **Type III galactosemia**
   
   The variety results from deficiency in galactose-6-phosphate epimerase. Its presentation may vary from a mild disease to a severe disease with cataract development, delayed development, and kidney disease.

Symptoms

Symptoms appear once milk is introduced to the infants.

- Failure to gain weight
- Convulsions
- Renal failure
- Cataracts
- Irritability
- Hypoglycemia
- Vomiting
- Lethargy
- Baby refuses to take feed
- Jaundice

Tests

- Blood culture
Red blood cells enzymatic activity
Urine analysis for ketones and reducing substances
Enzyme galactose-1-phosphate uridyl transferase measurement

**Treatment**

- Feed soy formula to infant.
- Lactose-free formula for infants.
- Calcium supplements.
- Avoid products that contain milk.

**Hereditary fructose intolerance**

This is a disorder characterized by the inability to metabolize fructose—a sugar present in fruits and juices. It arises from deficiency of the enzyme aldolase B leading to toxic accumulation of fructose.

**Etiology**

A genetic disorder arising from mutation of the ALDOB gene that encodes for the aldose B enzyme. The enzyme is mostly found in the liver where fructose metabolism takes place.

**Symptoms**

- Nausea
- Vomiting
- Severe hypoglycemia
- Diarrhea
- Seizures
- Lethargy
- Abdominal pain
- Irritability
- Excessive sleepiness

**Diagnosis**

Hepatomegaly, splenomegaly, and jaundice upon physical examination.

**Tests**

- Genetic testing
- Blood sugar levels - low
- Kidney function tests
- LFTs
- Enzymatic studies
- Blood clotting tests
- Liver biopsy
- Urinalysis
- Uric acid - high

**Treatment**

- Fructose- and sucrose-free diet.
- Complications are specifically treated.
Disorders of Amino Acid Metabolism

Amino acids are the building blocks of proteins, and disorders may arise from 1) the body’s inability to drive amino acids into the cells or 2) the inability to break down amino acids, leading to their accumulation.

Routing screening for the common disorders of amino acid metabolism entails
- Phenylketonuria
- Maple syrup urine disease
- Homocystinuria
- Tyrosinemia
- Alkaptonuria

Phenylketonuria

Phenylketonuria is an inherited disease that causes an increase in phenylalanine levels in the body. Phenylalanine is found in proteins and in some artificial sweeteners.

Pathophysiology

The disease arises from a defect in the PAH gene which is the gene encoding the enzyme phenylalanine hydroxylase needed for the conversion of phenylalanine to tyrosine that is later converted to epinephrine and norepinephrine. Defect in this enzyme leads to accumulation of phenylalanine and the resulting physiological manifestations.

PKU symptoms include
- Newborns do not present with symptoms
- Developmental delays
- Social issues
- Behavioral and emotional problems
- Intellectual disability
- Mental health issues
- Neurological disorders
- Low bone density
- Skin rashes (eczema)
- Musty odor in breath or urine
- Fair skin due to lack of melanin
- Blue eyes
- Microcephaly

Tests
- PKU screening
- Genetic testing

Treatment
- Low phenylalanine diet
- Avoid aspartame-containing products
- Use of fish oil
- Iron and carnitine supplements
Organic acidemia

This is a term that refers to a special group of genetic disorders of amino acid metabolism that involve branched chain amino acids that include leucine, isoleucine, and valine. The disorders result into accumulation of toxic acidic chemicals that cause adverse effects.

There are four main types of organic acidemia

1. Maple syrup urine disease
2. Isovaleric acidemia
3. Methylmalonic acidemia
4. Propionic acidemia

Maple syrup urine disease

Maple syrup urine disease (MSUD) is a hereditary disorder of protein breakdown leading to accumulation and poor protein utilization. The chemicals damage the brain, especially during episodes of infection or fevers. Urine from these patients has a characteristic smell similar to that of maple syrup—hence the name.

Symptoms:

- Vomiting
- Seizures
- Lethargy
- Coma
- Feeding difficulty
- Urine of affected individuals has maple syrup like smell.

Tests

Genetic testing, urine organic acid test, and plasma amino acid test are used to confirm the diagnosis.

Treatment

The treatment focuses on the general chronic condition and the acute metabolic decompensation that is common with the disorder.

- Dietary modification is the mainstay therapy that involves protein-free diet intake and use of a diet that is low in the amino acids leucine, valine, isoleucine which are the enzymes that aren’t broken down in these patients.
- In acute metabolic decompensation states, glucose infusions are needed as rapidly as possible, followed by insulin injections to promote anabolism. In the acute setting, the intake of branched-chain amino acids is stopped until their levels in circulation normalize.
- Surgical therapy using liver transplantation is successful in classic maple syrup urine disease with no neurologic symptoms.

Other types of organic academia

Isovaleric acidemia

- Sweaty foot odor
- Hepatomegaly
- Treated with Carnitine and Glycine
Propionic acidemia

- Alopecia
- Desquamation
- Corneal ulcers
- Hepatomegaly
- Treated with Carnitine

Methylmalonic acidemia

- HSM and acidosis
- Cardiomyopathy
- Renal damage

Treatment

- Vitamin B12 and Carnitine

References


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