BIOCHEMICAL GENETICS

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11 Biochemical genetics
• **Metabolic (or biochemical) genetics** involves the diagnosis and management of inborn errors of metabolism in which patients have enzymatic deficiencies that disturb biochemical pathways involved in metabolism of carbohydrates, amino acids, and lipids.

• Examples of metabolic disorders include galactosemia, glycogen storage disease, Lysosomal storage disorders, metabolic acidosis, paroxysmal disorders, Phenylketonuria, and urea cycle disorders.

we shall consider single-gene biochemical or metabolic diseases, including mitochondrial disorders.

At the beginning of the twentieth century Garrod introduced the concept of 'chemical individuality', leading in turn to the concept of the inborn error of metabolism. Beadle and Tatum later developed the idea that metabolic processes, whether in humans or any other organism, proceed by steps. They proposed that each step was controlled by a particular enzyme and that this, in turn, was the product of a particular gene. This was referred to as the 'one gene-one enzyme (or protein) concept'.

METABOLIC/BIOCHEMICAL GENETICS

• Metabolic (or biochemical) genetics involves the diagnosis and management of inborn errors of metabolism in which patients have enzymatic deficiencies that disturb biochemical pathways involved in metabolism of carbohydrates, amino acids, and lipids.

• Examples of metabolic disorders include galactosemia, glycogen storage disease, Lysosomal storage disorders, metabolic acidosis, paroxysmal disorders, Phenylketonuria, and urea cycle disorders.
Single gene defects result in abnormalities in the synthesis or catabolism of proteins, carbohydrates, or fats.

Most are due to a defect in an enzyme or transport protein, which results in a block in a metabolic pathway.

Effects are due to toxic accumulations of substrates before the block, intermediates from alternative metabolic pathways, defects in energy production and use caused by a deficiency of products beyond the block, or a combination of these metabolic deviations.
INBORN ERRORS OF METABOLISM

In excess of 200 inborn errors of metabolism are known which can be grouped either by the metabolite, metabolic pathway, function of the enzyme or cellular organelle involved (Table 11.1). Most inborn errors of metabolism are inherited in an autosomal recessive or X-linked manner with only a few being inherited in an autosomal dominant manner. This is because the defective protein in most inborn errors is an enzyme which is diffusible, and there is usually sufficient residual activity in the heterozygous state (i.e. loss-of-function mutation, p. 26) for the enzyme to function normally in most situations. If, however, the reaction catalysed by an enzyme is rate limiting (i.e. haploinsufficiency mutation, p. 26) or the gene product is part of a multimeric complex (i.e. dominant-negative mutation, p. 27), the disorder can manifest in the heterozygous state, i.e. be dominantly inherited (p. 105).

INBORN ERRORS OF METABOLISM

Can Be Divided into Two Groups Based on Cellular Localization and Clinical Presentation

Group 1

- **Predominantly cytoplasmic**
  - **Catabolism** of organic acids, amino acids, fatty acids and carbohydrates
  - Present acutely after a brief asymptomatic period
  - **Presentation** may include coma, respiratory distress, hypotonia, seizures, odor
INBORN ERRORS OF METABOLISM

Can be divided into two groups based on cellular localization and clinical presentation

• **Group 2**
  - Predominantly organelle
    - Lysosomal storage and mitochondrial
    - Have a more chronic course
  - Often do not present until late childhood or adulthood
INBORN ERRORS IN METABOLISM

**Group 1 - Cytoplasmic**
- Organic acidemias
  - Maple syrup urine disease
  - Pyruvate dehydrogenase
  - Fatty acid oxidation disorders
- Aminoacidopathies
  - Phenylketonuria
  - Urea Cycle disorders
  - Homocystinuria
- Carbohydrate metabolic disorders
  - Galactosemia
  - Glycogen storage disease

**Group 2 - Organelle**
- Lysosomal storage disorders
- Mitochondrial disorders
  (respiratory chain)

**ORGANIC-ACID DISORDERS**
Children affected with one of the organic acidemias present with periodic episodes of poor feeding, vomiting and lethargy in association with a severe metabolic, metabolic, low white cell (leukopenia) and platelet (thrombocytopenia) count, low blood sugar (hypoglycemia) and high blood ammonia levels (hyperammonemia). These episodes are often precipitated by intercurrent illness or increased protein intake, and after such an episode affected children can lose developmental skills. Analysis of blood from children at the time of these episodes reveals high levels of blood ammonia. Blood ammonia levels are extremely high in children with maple syrup urine disease. The two autosomal recessive organic-acid disorders methyimalonic acidemia (MMA) and propionic acidemia (PPA) are caused by deficiency of the enzymes methylmalonyl-CoA mutase and propionyl-CoA carboxylase, respectively. The enzyme deficiency results in accumulation of the toxic organic acids methylmalonic acid and propionic acid in the urine and other tissues. Dietary restriction of protein and long-chain fatty acids is extremely important in the treatment of these disorders. Therapy of the acute episode involves treatment of any infection, fluid replacement, correction of the metabolic acidosis and cessation of protein intake. Long-term prophylactic treatment involves restriction of protein intake, while some persons with methylmalonic acidemia are sensitive to biotin.

**DISORDERS OF AMINO-ACID METABOLISM**
There are a number of disorders of amino-acid metabolism, the best known of which is phenylketonuria.

**DISORDERS OF CARBOHYDRATE METABOLISM**
The inborn errors of carbohydrate metabolism can be considered in two main groups, disorders of monosaccharide metabolism and the glycogen storage disorders.

**LYSOSOMAL STORAGE DISORDERS**
In addition to the inborn errors of metabolism, in which an enzyme defect leads to deficiency of an essential metabolite and accumulation of intermediate metabolites, there are a number of disorders in which an accumulation of a macromolecule leads to its accumulation. This accumulation occurs because macromolecules are normally in a constant state of flux, with a subtle balance between their rates of synthesis and breakdown. Children born with lysosomal storage disorders are usually normal at birth, but with the passage of time, the accumulation of these abnormal metabolites leads to the clinical presentation of the disease. The clinical manifestations are usually the result of the accumulation of one or more of a variety of macromolecules.

**ORDERS AFFECTING MITOCHONDRIAL FUNCTION**
Mitochondrial disease was first identified in 1962 in a patient whose mitochondria showed mitochondrial abnormalities and there was loss of coupling between oxidation and phosphorylation. Over the last 40 years, it has become clear that the expression of clinical symptoms is not always associated with significant changes in mitochondrial morphology or function. Mitochondrial abnormalities are detectable in many tissues but the specific symptoms of mitochondrial disease are usually due to abnormalities in the respiratory chain. Mitochondrial disease is caused by mutations in mitochondrial DNA (mtDNA), which is inherited from the mother. Mitochondrial DNA contains genes for 13 proteins involved in the respiratory chain, 22 transfer RNAs and 2 ribosomal RNAs. The mitochondrial genome is located in the mitochondrial matrix and is circular, double-stranded DNA that is 16kb in size. The mitochondrial genome is organized into two distinct regions, the heavy (H) strand and the light (L) strand. The L strand is the maternal strand and the H strand is the paternal strand. The mitochondrial genome is transcribed into messenger RNA (mRNA) and then translated into protein. The translation process is initiated by oxidative phosphorylation (OXPHOS) and is mediated by the mitochondrial ATP synthase. The ATP synthase enzyme is composed of 13 subunits, 22 transfer RNAs and 2 ribosomal RNAs.

**THE 'COMPLEXES' ARE APTLY NAMED:**
The 'complexes' are aptly named. Analysis of complex I, for example, has revealed approximately 41 different subunits, of which some are homologous to enzymes in the cytoplasmic electron transport chain. Mitochondrial DNA is inherited maternally and is not subject to the same genetic drift that occurs in nuclear DNA. The mitochondrial genome is located in the mitochondrial matrix and is circular, double-stranded DNA that is 16kb in size. The mitochondrial genome is organized into two distinct regions, the heavy (H) strand and the light (L) strand. The L strand is the maternal strand and the H strand is the paternal strand. The mitochondrial genome is transcribed into messenger RNA (mRNA) and then translated into protein. The translation process is initiated by oxidative phosphorylation (OXPHOS) and is mediated by the mitochondrial ATP synthase. The ATP synthase enzyme is composed of 13 subunits, 22 transfer RNAs and 2 ribosomal RNAs.
INBORN ERRORS OF METABOLISM

• Frequency
  
  • **In the US:** The incidence, collectively, is estimated to be between 1 in 1400 and 1 in 5000 live births. The frequencies for each individual IEM vary, but most are very rare. Of term **infants who develop symptoms of sepsis without known risk factors**, as many as 20% may have an IEM.

  • **Internationally:** The overall incidence is similar to that of the United States. The frequency for individual diseases varies based on racial and ethnic composition of the population.
INBORN ERRORS OF METABOLISM

• Mortality/Morbidity:

  • IEMs can affect any organ system and usually affect multiple organ systems.

  • Manifestations vary from those of acute life-threatening disease to subacute progressive degenerative disorder.

  • Progression may be unrelenting with rapid life-threatening deterioration over hours, episodic with intermittent decompositions and asymptomatic intervals, or dangerous with slow degeneration over decades.
INBORN ERRORS OF METABOLISM

- **Race:**
  - The incidence within different racial and ethnic groups varies with predominance of certain IEMs within particular groups (e.g., cystic fibrosis, 1 per 1600 people of European descent; sickle cell anemia, 1 per 600 people of African descent; Tay-Sachs, 1 per 3500 Ashkenazi Jews).

- **Sex:**
  - The *mode of inheritance* determines the **male-to-female ratio** of affected individuals.
  
  - The **male-to-female ratio is 1:1** for autosomal dominant and autosomal recessive. It is also 1:1 for X-linked dominant if transmission is from mother to child.
INBORN ERRORS OF METABOLISM

- **Age for presentation of clinical symptoms varies** for individual IEM and variant forms within the IEM. The timing of presentation **depends on significant accumulation of toxic metabolites or on the deficiency of substrate.**

- The **onset and severity** may be worsen by **environmental factors such as diet and intercurrent illness.**
There are **two different types** of testing for metabolic conditions—screening tests and disease-specific diagnostic testing.

Screening tests allow you to detect the presence of a particular class of conditions and includes:

- **Serum electrolytes** (looking for evidence of acidosis), glucose & ammonia levels are also screening tests.
- **Blood** and urine amino acids for disorders of amino acid metabolism.
- Urine organic acids for disorders of organic metabolism acid.
- Acylcarnitine profile for disorders of fatty acid.
- Blood lactate and pyruvate for disorders of carbohydrate metabolism and mitochondrial disorders.
Specific diagnostic testing to measure activity of involved protein/enzyme is available for most conditions.

Often can be done on blood, but sometimes requires skin, liver or muscle biopsy.

DNA-based testing to identify disease-causing mutations is rapidly becoming available for many metabolic disorders.
DISORDERS OF AMINO ACID METABOLISM

- Amino acid metabolism disorders result from defects either in the synthesis of or the breakdown of amino acids or in the body’s ability to get the amino acids into cells. These disorders can be screened for by analysis of the amino acid content of urine. This screen is known as aminoaciduria.

- Many involve the accumulation of organic acid, acidosis, low glucose and elevated NH3

- Present with anion gap metabolic acidosis

- Results in altered mental status/lethargy in early childhood
METABOLIC DISORDERS OF AMINO ACID METABOLISM

- Maple syrup urine disease
- Urea cycle disorders
- Homocystinuria
- Phenylketonuria
<table>
<thead>
<tr>
<th>Predominant Biochemical Clinical Findings</th>
<th>Other</th>
<th>Most Common Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>KetoAcidosis Lethargy Odor</td>
<td>Ammonia: Normal or slightly elevated Ketones: Elevated Glucose: Normal</td>
<td>Maple syrup urine disease</td>
</tr>
<tr>
<td>Acidosis Lethargy Odor</td>
<td>Ammonia: Elevated Glucose: Normal or decreased Ketones: May be elevated Lactate: Slightly elevated</td>
<td>Methylmalonic acidemia Propionic acidemia Isolvaleric acidemia</td>
</tr>
<tr>
<td>Lactic Acidosis Lethargy</td>
<td>Acidosis: Usually present Ammonia: Normal or slightly elevated Ketones: May be elevated</td>
<td>Pyruvate dehydrogenase Pyruvate carboxylase deficiency Respiratory chain disorder</td>
</tr>
<tr>
<td>Hypoglycemia Lethargy</td>
<td>Ammonia: Lactate Acidosis Ketones: Absent or inappropriately low</td>
<td>Fatty acid oxidation defects</td>
</tr>
<tr>
<td>Hyperammonemia Lethargy</td>
<td>Acidosis: Absent Respiratory Alkalosis</td>
<td>Urea cycle disorders</td>
</tr>
</tbody>
</table>
**Clinical Presentation of Amino Acid Disorders**

<table>
<thead>
<tr>
<th>Clinical Abnormality</th>
<th>Abnormal Amino Acid</th>
<th>Presumptive Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute neonatal presentation with KetoAcidosis</td>
<td>Leucine, isoleucine, valine</td>
<td>Organic Acid Disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maple syrup urine disease</td>
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<tr>
<td></td>
<td></td>
<td>Methylmalonic acidemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Propionic acidemia</td>
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<td></td>
<td></td>
<td>Isovaleric acidemia</td>
</tr>
<tr>
<td>Acute neonatal presentation with Hyperammonemia</td>
<td>Arginine, Citruline</td>
<td>Urea cycle disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ornithine transcarbamylase deficiency</td>
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<tr>
<td></td>
<td></td>
<td>Argininosuccinate synthase deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Argininosuccinate lyase deficiency</td>
</tr>
<tr>
<td>Marfanoid, strokes, ectopia lentis, mental retardation</td>
<td>Homocystine &amp; methionine</td>
<td>Homocystinuria</td>
</tr>
<tr>
<td>Severe developmental delay</td>
<td>Phenylalanine</td>
<td>Phenylketonuria</td>
</tr>
</tbody>
</table>
HOMOCYSTINURIA

- This defect leads to a **multisystem disorder of the connective tissue, muscles, CNS, and cardiovascular system**

- characterized by **an accumulation of homocysteine in the serum** and **an increased excretion of homocysteine in the urine**. Infants appear to be normal and early symptoms, if any are present, are vague.

- Elevated homocystine levels affect collagens results in a Marfanoid habitus, ectopia lentis, mental retardation and strokes
There are **two forms** of Phenylketonuria

Most **common** form involves a **deficiency of phenylalanine hydroxylase**

**Rare** form involves **biopterin reductase deficiency**

**Treatment** of the two forms is **different and is effective**.

Is an **autosomal recessive condition** resulting from the accumulation of phenylalanine

Phenylalanine **is neurotoxic**

Results in **rapid decline of IQ** to 50 in first year if untreated due to neurotransmitter affects

Children with phenylketonuria (PKU), if untreated, are severely mentally retarded and often have convulsions. In PKU, the particular enzyme necessary for the conversion of phenylalanine to tyrosine, phenylalanine hydroxylase (PAH), is deficient. In other words there is a 'genetic block' in the metabolic pathway.

PKU was, in fact, the first genetic disorder in humans shown to be caused by a specific enzyme deficiency, by Jervis in 1953. As a result of the enzyme defect, phenylalanine accumulates and is converted into phenylpyruvic acid and other metabolites that are excreted in the urine. The enzyme block leads to a deficiency of tyrosine, with a consequent reduction in melanin formation. Affected children therefore often have blond hair and blue eyes (**Fig. 11.2**). In addition, areas of the brain that are usually pigmented, e.g. the substantia nigra, can also lack pigment.
PHENYLKETONURIA

• In PKU, particular enzyme necessary for the conversion of phenylalanine to tyrosine, phenylalanine hydroxylase (PAH), is deficient.

• As a result of the enzyme defect, phenylalanine accumulates and is converted into phenylpyruvic acid and other metabolites which are excreted in the urine.

• The enzyme block leads to a deficiency of tyrosine with a consequent reduction in melanin formation.

• Affected children therefore often have blond hair and blue eyes.
Figure 11.1 Sites of 'biochemical block' in phenylketonuria, alkaptonuria, congenital hypothyroidism and oculocutaneous albinism.
PHENYLKETONURIA-TREATMENT

- PKU could be treated by removal of phenylalanine from the diet. This way of treatment proved to be an effective treatment.

- If PKU is detected early enough in infancy, mental retardation (MR) can be prevented by giving a diet containing a restricted amount of phenylalanine.

- Phenylalanine is an essential amino acids and therefore cannot be entirely removed from the diet.

Treatment of PKU

An obvious method of treating children with PKU would be to replace the missing enzyme, but this cannot be done simply by any conventional means of treatment (p. 356). Bickel, only 1 year after the enzyme deficiency had been identified, suggested that PKU could be treated by removal of phenylalanine from the diet. This has proved to be an effective treatment. If PKU is detected early enough in infancy, mental retardation can be prevented by giving a diet containing a restricted amount of phenylalanine. Phenylalanine is an essential amino acid and therefore cannot be entirely removed from the diet. By monitoring the level of phenylalanine in the blood, it is possible to supply sufficient amounts to meet normal requirements and avoid levels that would result in mental retardation. Once brain development is complete dietary restriction can be relaxed-from adolescence onwards.
PHENYLKETONURIA - TREATMENT

• **By monitoring the level of phenylalanine in the blood**, it is possible to supply sufficient amounts to meet normal requirements and **avoid levels** which would result in MR.

• **MR seen in children with phenylketonuria** is most likely the result of an **elevation of phenylalanine** and/or its **metabolites** rather than a **deficiency of tyrosine**.
PHENYLKETONURIA-DIAGNOSIS

• newborns screening for PKU
  • This can be done by tests which detect the presence of the metabolite of
    • phenylalanine,
    • phenylpyruvic acid,
    in the urine or through elevated levels of phenylalanine in the blood.

Although PKU only affects approximately 1 in 10,000 persons of Western European origin, PKU was the first inborn error routinely screened for in newborns. This can be done by tests that detect the presence of the metabolite of phenylalanine, phenylpyruvic acid, in the urine by its reaction with ferric chloride or through elevated levels of phenylalanine in the blood. The latter test, known as the Guthrie test, involves taking blood samples from children in the first week of life and comparing the amount of growth induced by the sample with standards in a strain of the bacterium *Bacillus subtilis*, which requires phenylalanine for growth. This technique has been replaced by the use of a variety of biochemical assays of phenylalanine levels.

**Heterogeneity of hyperphenylalaninemia**

Elevated phenylalanine levels in the newborn period can be the result of causes other than PKU. A small proportion of newborn infants have a condition called benign hyperphenylalaninemia, caused by a transient immaturity of liver cells to metabolize phenylalanine; they do not require treatment as they are not at risk of developing mental retardation. There are, however, two other rare causes of hyperphenylalaninemia with serious consequences: in these two disorders the enzyme phenylalanine hydroxylase is normal but there is a deficiency of either dihydropteridine reductase or dihydrobiopterin synthetase. These two enzymes are involved in the synthesis of tetrahydrobiopterin, a cofactor necessary for normal activity of phenylalanine hydroxylase. Both disorders are more serious than classic PKU because there is a high likelihood of mental handicap despite satisfactory management of phenylalanine levels.
### PHENYLKETONURIA-MUTATION

- Although all cases of classical PKU arise from a deficiency of phenylalanine hydroxylase, more than **70 different mutations** in the PAH gene have now been identified.

- Certain mutations are more common in persons with PKU from specific population groups.

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**Mutational basis of PKU**

Although all cases of classic PKU arise from a deficiency of phenylalanine hydroxylase, more than 450 different mutations in the PAH gene have now been identified. Certain mutations are more common in persons with PKU from specific population groups. In addition, in persons of Western European origin with PKU, the mutations occur on a limited number of DNA haplotypes. Interestingly, however, a variety of different individual mutations have been found in association with some of these haplotypes.
MATERNAL PHENYLKETONURIA

• Children born to mothers with phenylketonuria have an increased risk of MR even when their mothers are on closely controlled dietary restriction.

• The reduced ability of the mother with PKU to deliver an appropriate amount of tyrosine to her fetus in uterus could result in reduced fetal brain growth.

Maternal phenylketonuria

Children born to mothers with phenylketonuria have an increased risk of mental retardation even when their mothers are on closely controlled dietary restriction (p. 161). It has been suggested that the reduced ability of the mother with PKU to deliver an appropriate amount of tyrosine to her fetus in utero could result in reduced fetal brain growth.
DISORDERS OF CARBOHYDRATE METABOLISM

- Galactosemia
- Glycogen Storage Disorders

The inborn errors of carbohydrate metabolism can be considered in two main groups, disorders of monosaccharide metabolism and the glycogen storage disorders.
DISORDERS OF MONOSACCHARIDE METABOLISM

Two examples of disorders of monosaccharide metabolism are galactosemia and hereditary fructose intolerance.

Galactosemia

Galactosemia is an autosomal recessive disorder due to deficiency of the enzyme galactose-1-phosphate uridyl transferase, which is necessary for the metabolism of the dietary sugar galactose. Newborn infants with galactosemia present with vomiting, lethargy, failure to thrive and jaundice in the second week of life. If untreated, they go on to develop complications that include mental retardation, cataracts and cirrhosis of the liver. Galactosemia can be screened for by the presence of reducing substances in the urine with specific testing for galactose. The complications of galactosemia can be prevented by early diagnosis and feeding of affected infants with milk substitutes that do not contain galactose or lactose, the sugar found in milk, which is broken down into galactose. Early diagnosis and treatment are essential if the severe complications are to be prevented.
GALACTOSEMIA

• Findings include: liver failure with lactic acidosis & coagulopathy, hemolytic anemia, renal tubular dysfunction with proteinuria

• Neutrophil dysfunction results in infection - E. Coli sepsis

• If not treated by galactose dietary restriction early mortality is very high

• Histologically liver shows hepatocellular loss, with extensive fibrosis

• At high power cholestasis (Suppression of biliary flow) with ductal proliferation, steatosis (Accumulation of fat) and extensive fibrosis
Liver in patient dying of Galactosemia Hepatocellular loss, cholestasis, steatosis due to activation of FA production and fibrosis
GLYCOGEN STORAGE DISORDERS

• Disturbance in the breakdown or synthesis of glycogen

• There are many enzymes regulating glycolysis and many different glycogen storage diseases

• They can be generally categorized into hepatic and myopathic forms based on the localization of the involved enzyme which determines the organs effected

• Complex carbohydrate diet helps control complications

• Enzyme replacement is available

Hereditary fructose intolerance

Hereditary fructose intolerance is an autosomal recessive disorder due to deficiency of the enzyme fructose-1-phosphate aldolase. Dietary fructose is present in honey, fruit and certain vegetables, and in combination with glucose in the disaccharide sucrose in cane sugar. Individuals with hereditary fructose intolerance present at different ages, depending on when fructose is introduced into the diet. Symptoms can be minimal but might also be as severe as those seen in galactosemia which include failure to thrive, vomiting, jaundice and convulsions. The diagnosis is confirmed by the presence of fructose in the urine and enzyme assay on an intestinal mucosal or a liver biopsy sample. Dietary restriction of fructose is associated with a good long-term prognosis.
GLYCOGEN STORAGE DISORDERS
GLYCOGEN STORAGE DISORDERS

• Glycogen storage disorders (GSD) are a group of inherited inborn errors of metabolism due to deficiency or dysfunction of these enzymes.

• Glycogen synthesis errors result in decreased normal glycogen ± deposition of abnormally branched glycogen chains.

• Degradation errors block formation of glucose from glycogen, leading to hypoglycemia and pathological accumulation of glycogen in the tissues (Heart & Liver).
**GLYCOGEN STORAGE DISORDERS**

• These metabolic errors **can be confined** to just liver and **muscle** but some cause more generalized pathology and affect **tissues such as the kidney, heart and bowel.**

• There are **over 6 types of GSD** and they are classified based on the enzyme deficiency and the affected tissue.

• All type of GSD are inherited as **autosomal recessive.**

**GLYCOGEN STORAGE DISEASES**

Glycogen is the form in which the sugar glucose is stored in muscle and liver as a polymer, acting as a reserve energy source. In the glycogen storage diseases (GSDs) glycogen accumulates in excessive amounts in skeletal muscle, cardiac muscle and/or liver due to a variety of inherit errors of the enzymes involved in synthesis and degradation of glycogen. In addition, because of the metabolic block, glycogen is unavailable as a normal glucose source. This can result in hypoglycemia, impairment of liver function and neurological abnormalities.

In each of the six major types of GSD there is a specific enzyme defect involving one of the steps in the metabolic pathways of glycogen synthesis or degradation. The various types can be grouped according to whether they affect primarily the liver or muscle. All six types are inherited as autosomal recessive disorders, although there are variants of the hepatic phosphorylase which are X-linked.

**Glycogen storage diseases that primarily affect liver**

**von Gierke disease (GSD I)**

Von Gierke disease was the first described disorder of glycogen metabolism and is due to deficiency of the enzyme glucose-6-phosphatase, which is responsible for degradation of liver glycogen to release glucose. Affected infants present with an enlarged liver (hepatomegaly) and/or sweating and a fast heart rate due to hypoglycemia, which can occur after feeding at any time during. Treatment is simple: frequent feeding and the avoidance of fasting to maintain the blood sugar.

**Cori disease (GSD III)**

Cori disease is caused by deficiency of the enzyme amylo-1,6-glucosidase, which is also known as the debrancher enzyme. Deficiency of the enzyme results in glycogen accumulation in the liver and other tissues resulting from the inability to cleave the branching links of the glycogen polymer. Affected infants present with hypoglycemia because of glycogen accumulation and muscle weakness. Treatment involves avoiding hypoglycemia by frequent feeding and avoiding prolonged periods of fasting.

**Andersen disease (GSD IV)**

Andersen disease results from deficiency of glycogen transfer enzyme which leads to formation of abnormal glycogen consisting of long chains with few branches which cannot be broken down by the enzymes normally responsible for glycogen degradation. Affected infants present with hypoglycemia and abdominal pain. In the first year of life, the liver often progresses to liver failure. No effective treatment is available apart from the possibility of a liver transplant.

**Hepatic phosphorylase deficiency (GSD VI)**

Hepatic phosphorylase is a multimeric enzyme complex with subunits coded for by both autosomal and X-linked genes. Deficiency of hepatic phosphorylase leads to glycogen accumulation due to the deficiency of the lysosomal enzyme α-1,4-glucosidase that is needed to break down glycogen. Treatment involves carbohydrate supplements that improve growth.

**Glycogen storage diseases that primarily affect muscle**

**Pompe disease (GSD II)**

Infants with Pompe disease usually present in the first months of life with floppy (hypotonia) and delay in the gross motor milestones because of muscle weakness. They then develop an enlarged heart and die of cardiac failure in the first or second year. Voluntary and cardiac muscle accumulates glycogen due to the deficiency of the lysosomal enzyme α-1,4-glucosidase that is needed to break down glycogen. The diagnosis can be confirmed by enzyme assay on white blood cells or fibroblasts. Early reports of enzyme replacement therapy appear promising.

**McArdle disease (GSD V)**

Persons with McArdle disease present with muscle cramps on exercise. It is caused by a deficiency of muscle phosphorylase, which is necessary for degradation of muscle glycogen. There is no effective form of treatment, although in some affected individuals the muscle cramps tend to decline if exercise is continued, probably as a result of other energy sources becoming available from alternative metabolic pathways.
In addition to the inborn errors of metabolism, in which an enzyme defect leads to deficiency of an essential metabolite and accumulation of intermediate metabolic precursors, there are a number of disorders in which a deficiency of a lysosomal enzyme involved in the degradation of complex macromolecules leads to their accumulation. This accumulation occurs because macromolecules are normally in a constant state of flux, with a delicate balance between their rates of synthesis and breakdown. Children born with lysosomal storage diseases are usually normal at birth but with the passage of time commence a downhill course of differing duration to owing the accumulation of one or more of a variety or type of macromolecules.
LYSOSOMAL STORAGE DISORDERS

• The lysosome is commonly described as the cell’s recycling center because it processes unwanted material into substances that the cell can utilize.

• Lysosomes break down this unwanted substance via enzymes.

• Lysosomal disorders are triggered when a particular enzyme exists in too small amount or is missing altogether.
When this happens, **substances accumulate in the cell**. In other words, when the **lysosome doesn’t function normally**, excess products destined for breakdown and recycling are stored in the cell.

This is why Lysosomal Disease is often referred to as Lysosomal Storage Disorders.
LYSOSOMAL STORAGE DISORDERS

• Lysosomal Storage Disorders are relatively rare and together have an incidence of 1 in 7000-8000 live births.
• All lysosomal disorders originate from an abnormal accumulation of substances inside the lysosome.
• Lysosomal Storage Disorders affect mostly children and they often die at a young and unpredictable age, many within a few months or years of birth. Many other children die of this disease following years of suffering from various symptoms of their particular disorder.
• The **symptoms** of Lysosomal Disease **vary**, depending on the particular disorder and other variables like the **age of onset**, but they are **always shocking**.
• They can include developmental delay, movement disorders, seizures, dementia, deafness and/or **blindness**.
• Some people with Lysosomal Disease **have enlarged livers** and **spleens**, **pulmonary** and **cardiac problems**, and **bones that grow abnormally**.
The Lysosomal storage diseases are classified by the nature of the primary stored material involved, and can be broadly broken into the following:

- lipid storage disorders, mainly sphingolipidoses (including Gaucher's diseases and Tay-Sachs disease)
- mucopolysaccharidoses (including Hunter syndrome)
MITOCHONDRIAL DISORDERS

- Classically involve mutations in mitochondrial DNA
- Follow a maternal pattern of inheritance
- Highly variable with regard to penetrance and expressivity based on the variability in tissue distribution of abnormal mitochondria
- Involve global abnormality in aerobic metabolism

MITOCHONDRIAL ENCEPHALOMYOPATHY, LACTICE ACIDOSIS AND STROKE-LIKE EPISODES (MELAS)

First delineated in 1984, this extremely variable condition is now recognized as one of the commonest mitochondrial disorders. Short stature may be a feature, but it is stroke-like episodes that mark out this particular mitochondrial disorder, though these episodes do not necessarily occur in all affected family members. When they do occur, they may manifest as vomiting, headache, or visual disturbance, and sometimes lead to transient hemiplegia or hemianopia. A common presenting feature of MELAS is type 2 diabetes mellitus, and a sensorineural hearing hearing loss may also occur (described as maternally inherited diabetes and deafness [MIDD]). These latter clinical features are associated with the most common mutation, which is an A>G substitution at position 3243, which affects tRNA leucine\(^{\text{UUR}}\). This is found in about 80% of patients, followed by a T>C transition at position 3271, also affecting tRNA leucine\(^{\text{UUR}}\).
MITOCHONDRIAL DISORDERS

• Growth impairment, development delay & multiple organ dysfunction for tissue dependent on aerobic metabolism
• Common abnormalities include myoclonic seizures & myopathy
• Elevated blood lactate and pyruvate
Thank you