Rey's syndrome & Inborn errors of metabolism affecting the liver

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1. **Reye's Syndrome**
2. **Wilson disease**
3. **Hemochromatosis**
4. **Glycogen Storage Disease:**

Type I: von Gierke’s disease.

Type II: acid maltase deficiency or Pompe disease.

Type III: Forbes-Cori disease or limit dextrinosis.

Type IV: amylopectinosis or Andersen disease

Metabolic disorders

- Metabolic disorders are diseases that disrupts metabolism.
- A metabolic disease is most frequently caused by an absence or deficiency in an enzyme (or protein).
- Inborn errors of metabolism are heritable disease due to defective gene or genes that are present at birth.
- When one of the enzymes is not working properly, the process of breaking down of specific foods can go more slowly or shut down completely.

Reye's Syndrome

- Reye syndrome is not a genetic disease.
- Extremely rare syndrome that causes brain swelling and liver damage.
- Most commonly affect kids between 4 and 14 years old recovering from a viral infection
- Studies strongly linked the use of aspirin or aspirin-containing medications during viral disease to develop Reye's syndrome.
- The mechanism by which aspirin and other salicylates trigger Reye's syndrome is not completely understood.
- Reye syndrome is a potentially life threatening disorder that should be treated as a medical emergency.
- Early detection and treatment are critical — the chances for a successful recovery increase greatly when Reye syndrome is treated in its earliest stages.

- **Diagnosis**
- 1. Blood sugar usually drops due to liver damage
- 2. Levels of ammonia rise due to hepatic dysfunction that leads to a failure in the urea cycle.
- 3. The liver also may swell, and fats may build up.
- 4. Swelling may occur in the brain.
- 5. There is usually no fever.
- 6. Seizures or loss of consciousness, diarrhea, rapid breathing, being sleepy or sluggish, aggressive or irrational behavior and vomiting that doesn't stop

- **Pathophysiology**
- Mitochondrial dysfunction that inhibits oxidative phosphorylation and fatty-acid beta-oxidation
- All cells have swollen mitochondria that are in reduced number, along with glycogen depletion and minimal tissue inflammation.

- Salicylates and metabolites from the virus induce the opening of a high-conductance, cyclosporin-sensitive pore in the mitochondrial inner membrane. This causes swelling, depolarization, and uncoupling of oxidative phosphorylation.

Treatment

- There is no cure for RS.
- Successful management aimed at protecting the brain against irreversible damage by reducing brain swelling, preventing complications in the lungs, and anticipating cardiac arrest.
- **What is the prognosis?**
- Recovery is directly related to the severity of the swelling of the brain.
- Some people recover completely, while others may sustain varying degrees of brain damage.
- When RS is diagnosed and treated in its early stages, chances of recovery are excellent. When diagnosis and treatment are delayed, the chances for successful recovery and survival are severely reduced.
- Unless RS is diagnosed and treated successfully, death is common, often within a few days.

Wilson disease

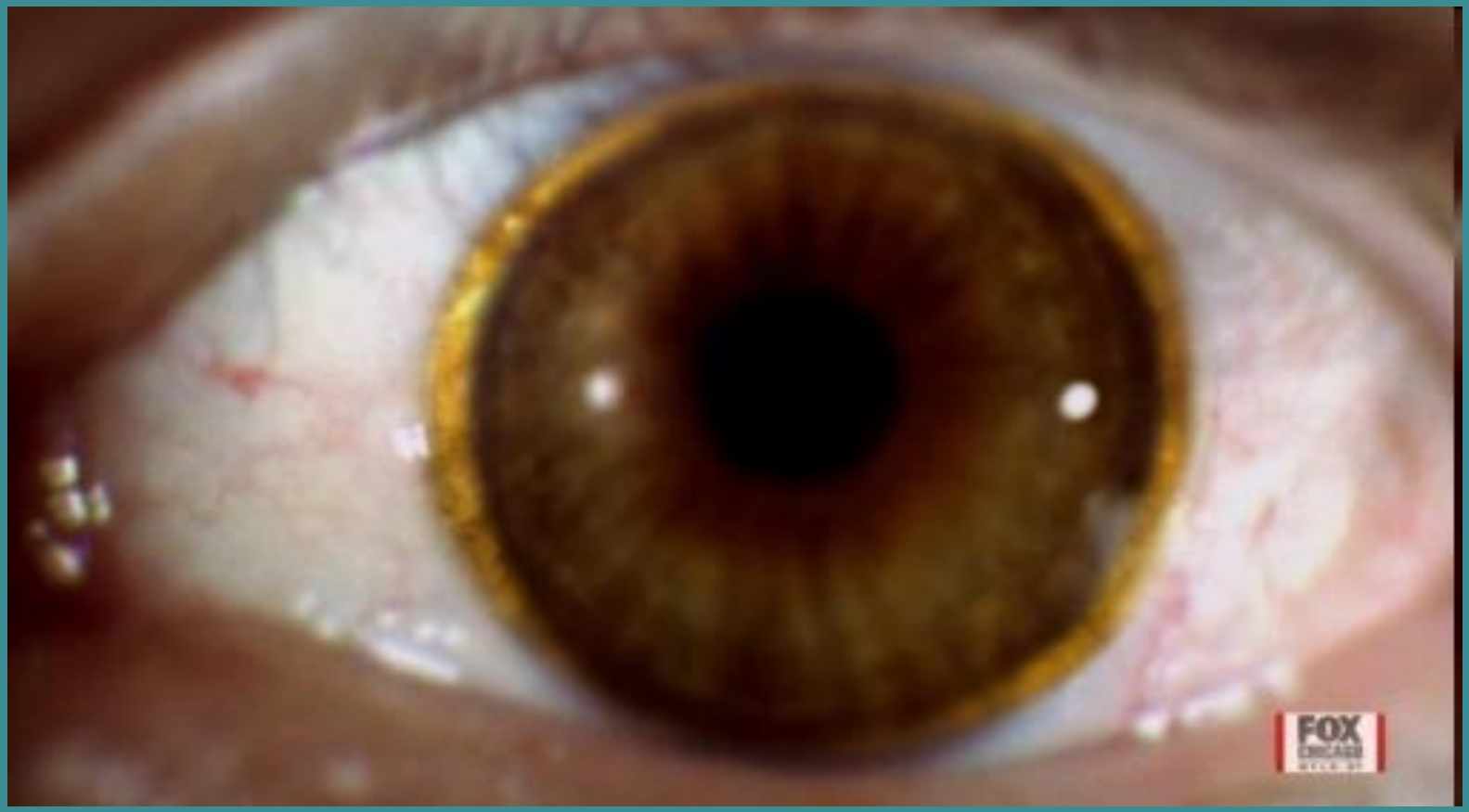
- It is autosomal recessive genetic disease that prevents the body from getting rid of extra copper.
- People who get Wilson disease inherit two abnormal copies of the **ATP7B** gene, one from each parent. Wilson disease carriers, who have only one copy of the abnormal gene, do not have symptoms.
- Normally, copper from the diet is filtered out by the liver and released into bile.
- In WD when the copper storage capacity of the liver is exceeded, copper is released into the bloodstream and travels to other organs—including the brain, kidneys, and eyes. Over time, high copper levels can cause life-threatening organ damage.
- About 1 in 40,000 people get Wilson disease. It equally affects men and women.
- Symptoms usually appear between ages 5 to 35.

- **What are the symptoms of Wilson disease?**
- Wilson disease first attacks the liver, the central nervous system, or both.
- In Liver or spleen: swelling, yellowing of the skin and whites of the eyes. Rarely, acute liver failure
- In CNS: problems with speech, swallowing, or physical coordination.

- Other signs and symptoms: anemia, low platelet or white blood cell count, slower blood clotting, measured by a blood test.

- **Kayser-Fleischer rings** is the most unique sign of Wilson disease that result from a buildup of copper in the eyes. They appear in each eye as a rusty-brown ring around the edge of the iris and in the rim of the cornea.

Kayser-Fleischer rings (KF rings) Wilson Disease



Treatment

- Requires lifelong treatment to reduce copper in the body.

- **Initial therapy includes**

1- The removal of excess copper using drugs like (d-penicillamine and trientine)

2- A reduction of copper intake (food rich in cooper include beef liver, nuts, seeds, dark chocolate).

3- The treatment of any liver or central nervous system damage.

Hemochromatosis

- Caused by too much absorption and storage of iron.
- Healthy people absorb about **10** percent of the iron in the food, People with hemochromatosis absorb up to **30** percent of iron. Over time, they absorb and retain between **5 to 20** times more iron than the body needs.

- Our body has no natural way to rid itself of the excess iron, it is stored in body tissues, specifically the liver, heart, and pancreas.

Causes

- Hemochromatosis is an autosomal recessive disease results from defect in a gene called **HFE** located at the short arm of chromosome 6.
- The HFE protein regulates the production of a protein called hepcidin which is produced by the liver, and it determines how much iron is absorbed from the diet and released from storage sites in the body.
- The most known mutation of HFE is C282Y.
- In people who inherit C282Y from both parents, the body absorbs too much iron and hemochromatosis can result.
- Those who inherit the defective gene from only one parent are carriers for the disease but usually do not develop it; however, they still may have higher than average iron absorption.

Diagnosis

1. **Serum transferrin saturation:** A plasma protein that transport iron in blood. Transferrin saturation values greater than 45 percent are considered too high.
2. **Ferritin.** intracellular protein that stores and releases iron in controlled way. This test measures the amount of iron stored in your body (most of ferritin is in liver).

Normal range of ferritin

- Female 15-205 ng/mL (nanograms per milliliter)
- Male 30-566 ng/mL
- Children's age 6 months to 15 years 12-140 ng/mL

3. Genetic testing to confirm the diagnosis blood test to detect the HFE mutation, which will confirm the diagnosis.

Treatment

- Phlebotomy, which means removing blood the same way it is drawn from donors at blood banks.
- The goal of phlebotomy is to reduce your iron levels to normal. The amount of blood removed and how often it's removed depend on your age, your overall health and the severity of iron overload. It may take a year or longer to reduce the iron in your body to normal levels.
- **Initial treatment** Initially, you may have a pint (about 470 milliliters) of blood taken once a week
- **Maintenance treatment schedule.** Once your iron levels have returned to normal, blood can be removed less often, typically every two to four months. The schedule depends on how rapidly iron accumulates in your body.
- Blood ferritin levels will be tested periodically to monitor iron levels.

Glycogen Storage Disease

- Result from storage of abnormal quantities of glycogen or storage of glycogen with abnormal properties.
- Deficiencies of enzymes related to glycogen metabolism, affect the levels of glucose and glycogen because their deficiency can significantly alter the normal metabolism of glucose.

Type I Glycogen Storage Disease

- also known as von Gierke's disease, is the most common form of glycogen storage disease, accounting for 25% of all cases.
- **Cause** inherited deficiency of liver Glucose 6- phosphatase (release free glucose & phosphate).
- G6P-ase is not found in the muscles.
- The liver glycogen is normal in structure but present in abnormally large amounts.

- The absence of glucose 6-phosphatase in the liver causes hypoglycemia due to inability to release free glucose.

- The presence of excess glucose 6-phosphate triggers an increase in glycolysis in the liver, leading to a high level of lactate and pyruvate in the blood.
- Patients who have von Gierke disease also have an increased dependence on fat metabolism.

Four types of GSD I

The activity of G6P-ase activity is associated with three transport proteins (T1, T2, T3) that facilitate movement of glucose-6-phosphate (G6P)

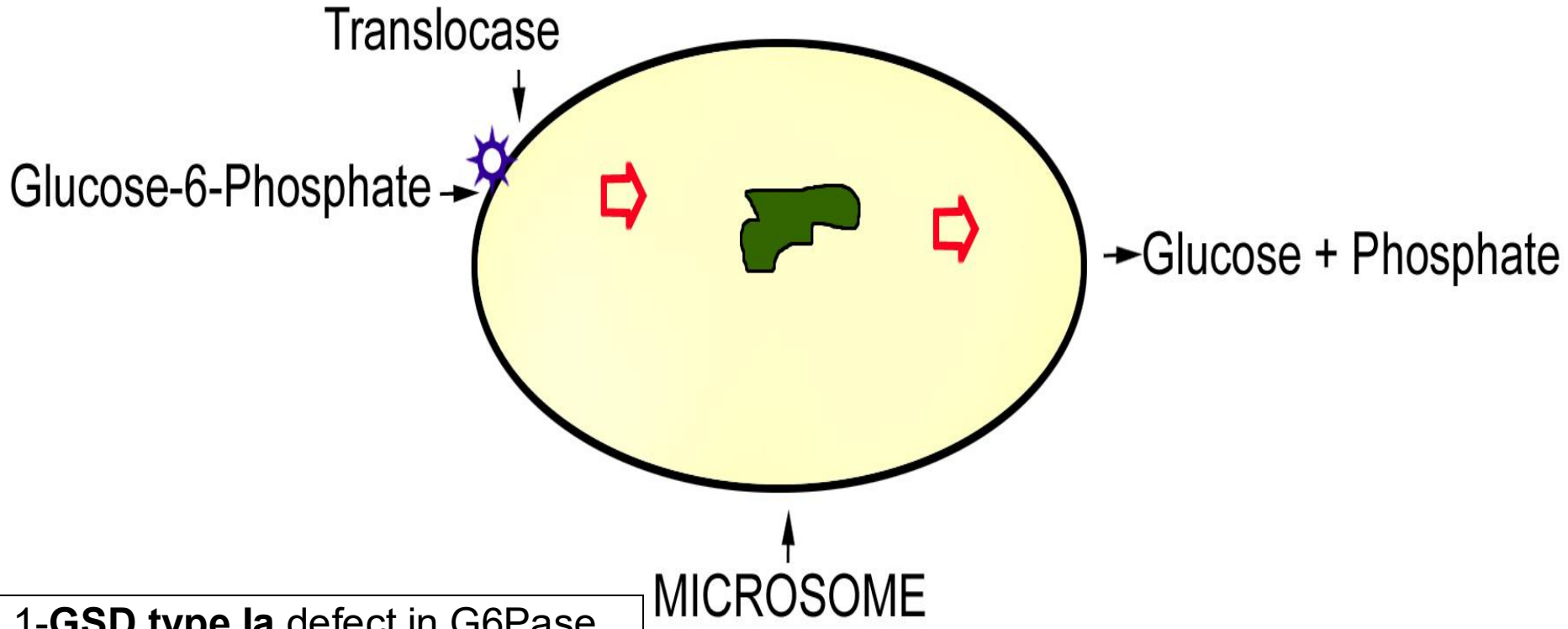
- The microsomal G6Pase system consists of membrane-bound phosphohydrolase and various translocases for G6P (T1), phosphate (T2), and glucose (T3).

1-**GSD type Ia** caused by G6Pase defect

2- **GSD type Ib** resulting from deficiency of a specific translocase T1 which is a transporter of glucose-6-phosphate (G6P) into the microsomal compartment

3-**GSD type Ic** is deficiency of translocase T2 that carries inorganic phosphates from microsomes into the cytosol

4- **GSD type Id** is deficiency in a T3 that translocates free glucose molecules from microsomes into the cytosol.



1-**GSD type Ia** defect in G6Pase
2-**GSD type Ib** deficiency T1
3-**GSD type Ic** deficiency of T2
4-**GSD type Id** deficiency in a T3

- **Glycogen storage disease type II**

- known as acid maltase deficiency or Pompe disease, is a lysosomal disease.
- It is an autosomal recessive disease that causes accumulation of glycogen inside lysosomes within cardiac and skeletal muscle tissue and other tissues causing their damage.
- Deficiency of a lysosomal enzyme known as acid alpha-1,4-glucosidase, (also known as acid maltase) causes accumulation of glycogen in lysosome known as GSD type II.
- Alpha-1,4-glucosidase is important for the degradation of glycogen in the lysosome thus its absence causes accumulation of glycogen that leads to impairment of striated muscular cells and cardiac muscle and diaphragm.
- = infantile form begins within months of birth, characterized by heavy deposits of glycogen in the heart, liver, and tongue; causing their enlargement
- The hypotonia (low muscle tone tension or resistance to stretch) **and** muscle weakness (myopathy) involve skeletal and respiratory muscles as well with progressive respiratory insufficiency.
- In the CNS, the disease primarily affects the nuclei of the brainstem and the cells of the ventral horn of the spinal cord. Mental functions are preserved.
- = Juvenile and adult forms, occur in childhood or adulthood is characterized by glycogen deposition in skeletal muscles. The involvement of the cardiac muscle varies in the juvenile form, the muscle is unaffected in the adult form
- No cure for this disease however Enzyme Replacement Therapy (ERT) using apha glucosidase is the treatment to remove excess glycogen.

- **Glycogen storage disease type III**
- also known as Forbes-Cori disease or limit dextrinosis.
- Both liver and skeletal muscles are involved in GSD type III.
- Deficiency of the cytosolic debrancher enzyme causes GSD type III.
- Abnormal glycogen with short external branches is stored in the liver, heart, and skeletal muscle cells.

- Two forms of the disease exist.

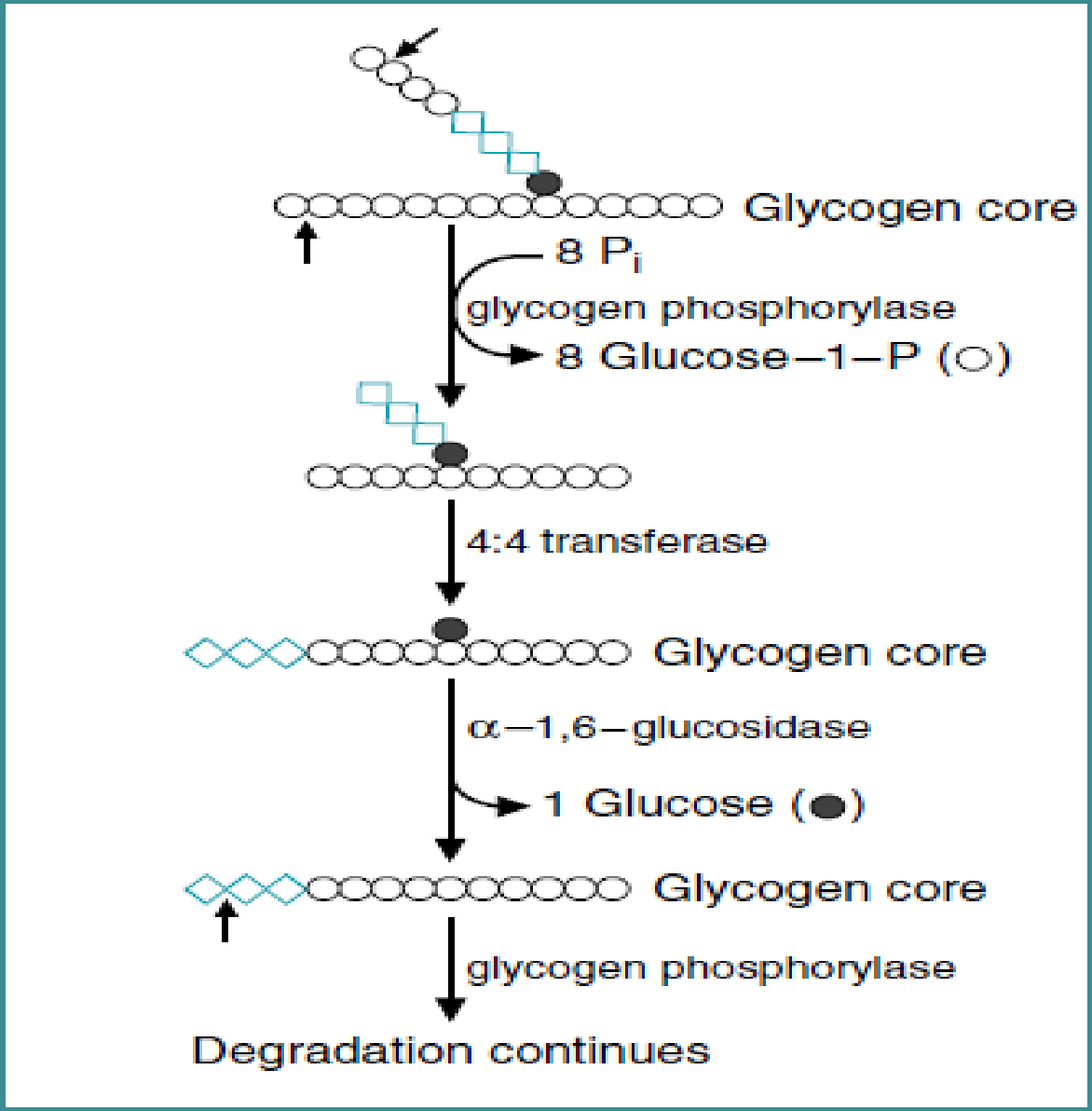
1- In GSD type IIIa, the liver, skeletal muscles, and cardiac muscle are involved.

2- In GSD type IIIb, only the liver is involved.

Glycogen storage disease type III

Deficiency of the cytosolic debrancher enzyme

The debrancher enzyme, catalyzes the removal of the last branched four residues. It has two catalytic activities it acts as a
1- As a transferase, it first removes the three glucose residues, and adds it to the end of a longer chain.
2- Alpha amylo-1,6-glucosidase activity resulting in the release of free glucose.



- **Glycogen storage disease type IV**
- also known as amylopectinosis or Andersen disease, is a rare disease that leads to early death
- **Causes** deficiency in amylo-4:6-transferase (branching enzyme).

- Accumulation of abnormally structured glycogen in the liver, heart, and neuromuscular system characterizes this disease.
- The abnormal glycogen has long external branches that resemble amylopectin.
- This form of glycogen is less soluble; liver cirrhosis probably arises as a reaction to this insoluble material.

Glycogen storage disease type IV

Deficiency in amylo-4:6-transferase

When the chain reaches 11 residues or more in length, then 6 to 8 residue piece is cleaved by amylo-4:6-transferase and reattached to a glucose unit by an α-1,6 bond.