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DEPT: HUMAN BIOLOGY

COURSE: HMB 401

ASSIGNMENT: Discuss in Details the Inborn Error of Metabolism of Cori Disease.

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

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( low blood sugar).

Glycogen Storage Disease Type III ( Cori Disease).

is an autosomal recessive metabolic disorder and inborn error of metabolism  (specifically of carbohydrates) characterized by a deficiency in glycogen de branching enzymes.

Other names include for cori Forbesdisease in honor of clinician Gilbert Burnett Forbes (1915–2003), an American physician who further described the features of the disorder, or limit dextrinosis, due to the limit dextrin-like structures in cytosol limit dextrin is the remaining polymer produced after hydrolysis of glycogen. Without glycogen debranching enzymes to further convert these branched glycogen polymers to glucose, limit dextrinosis abnormally accumulates in the cytoplasm.

Glycogen is a molecule the body uses to store carbohydrate energy. Symptoms of GSD-III are caused by a deficiency of the enzyme amylo-1,6 glucosidase, or debrancher enzyme.This causes excess amounts of abnormal glycogen to be deposited in the liver, muscles and, in some cases, the heart

Causes

GSD-III is an inborn error of metabolism caused by mutations in the *AGL* gene that is located on chromosome 1p21. The *AGL*gene is responsible for the production of the debranching enzyme.

Glycogen is stored in the liver and muscles for future energy needs. Glycogen can then be converted into sugar (glucose). Glucose is used as a readily available source of energy during fasting or exercise. The debranching enzyme has two active (catalytic) sites called amylo-1,6-glucosidase and 4-alpha-glucanotransferase. Both sites on the enzyme are together with the phosphorylase and phosphorylase kinase enzymes (impaired in GSD types VI and IX, respectively)responsible for breaking down glycogen to raise the blood sugar concentration. Without normal debranching enzyme function, two changes take place. If glycogen can only be broken down partially, an insufficient amount of energy/glucose can be produced. The structure that is left, resembling a molecule called a “limit dextrin”, is excessively stored in liver, and (skeletal and cardiac) muscle tissues.

**Classification**

There are four subtypes of GSD-III:

GSD-IIIa is the most common type, affecting 85%, and affects both the liver and (cardiac and/or skeletal) muscles.

GSD-IIIb affects about 15% of individuals and only affects the liver. AGL molecular testing can display mutations specific to GSD-IIIb.

GSD-IIIc is extremely rare and believed to be caused by loss of activity of the glucosidase active site of the glycogen debranching enzyme.

GSD-IIId is extremely rare and believed to be caused by loss of activity of the transferase active site of the glycogen debranching enzyme.

Diagnosis

Glycogen storage disease type III starts during infancy with hypoglycemia  and failure to heal.

Clinical examination usually reveals Hepatomegaly, Muscular diseases including hypotonia, and cardiomyopathy usually occurs later. The liver pathology typically relapses as the individual enter adolescence as does splenomegaly, should the individual develop it.

Most common presenting symptoms are enlarged liver (hepatomegaly) (98%), low blood sugar (hypoglycemia) (53%), failure to heal(49%) and recurrent illness and/or infections (17%). Symptoms and signs of GSD-III, at least during the first 4 to 6 years of life, may be indistinguishable from GSD type I. The amount of glycogen in the liver and muscles is abnormally high, the liver is enlarged, and the abdomen protrudes. The muscles tend to be flaccid or weak.

A typical child with GSD-III has short stature, low blood sugar after fasting that does not respond to the hormone glucagon, and an elevated level of fatty substances in the blood, known as hyperlipidemia. Hypoglycemia is usually associated with increased ketone bodies, and ketonemia can precede hypoglycemia, reflecting activation of burning fat stores. Patients with GSD-III may also have difficulty fighting infections, and may experience unusually frequent nosebleeds. Enlarged heart muscle (cardiac hypertrophy) is common in individuals with GSD-IIIa and can already appear in early childhood. However, in most children, heart function remains within normal limits. Children with GSD-III often grow slowly during childhood and puberty may be delayed, but their adult height is usually normal. Most signs and symptoms improve significantly with adequate dietary management.

In adulthood, the liver manifestations of the disease usually subside, but progression to liver scarring (cirrhosis) and malignancy (carcinoma) may occur. Despite dietary management, muscle disease can get worse. As the unit of adult GSD-III patients is still relatively young and small, the course of the disease over time is incompletely described.

Some affected individuals may have virtually no symptoms (asymptomatic) other than a protruding abdomen and an enlarged liver in childhood. These patients tend to lose these few symptoms during adolescence when their liver decreases progressively in size. Other forms of diagnosis include:

* Biopsy(muscle or liver)
* CBC( complete blood count)
* Ultrasound
* DNA mutation analysis (helps ascertain GSD III subtype)

Treatment

Treatment for glycogen storage disease type III may involve a high-protein diet, in order to facilitate gluconogenesis. Further more, the individual may need:

* IV(intravenous)glucose  (if oral route is inadvisable)
* Nutritional specialist
* Vitamin D(for osteoporosis/secondary complication)
* Hepatic transplant (if complication occurs).
* Good dietary control includes at home monitoring of blood glucose and ketones. Based on clinical observations, it is believed that the diet can prevent or resolve heart and/or muscle disease.

Liver transplantation is indicated only for patients with severe hepatic cirrhosis, liver dysfunction and /or liver cancer (hepatocellular carcinoma).

In regards to genetics, glycogen storage disease type III is inherited in an autosomal recessive pattern (which means both parents need be a carrier), and occurs in about 1 of every 100,000 live births. The amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase gene and mutations to it, are at the root of this condition. The gene is responsible for creating glycogen debranching enzyme , which in turn helps in glycogen decomposition.

GSD-III is a genetic disorder characterized by variable liver, cardiac muscle and skeletal muscle abnormalities. Symptoms are associated with abnormalities in the *AGL* gene, causing deficiency of the glycogen debranching enzyme. GSD-III is inherited as an autosomal recessive trait.

Recessive genetic disorders occur when an individual inherits two copies of an altered gene for the same trait, one from each parent. If an individual inherits one normal gene and one gene for the disease, the person will be a carrier for the disease but usually will not show symptoms. The risk for two carrier parents to both pass the altered gene and have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents is 25%. The risk is the same for males and females.

All individuals carry mutations/variants in ± 4-5 genes. Parents who are close relatives (consanguineous) or who originate from closed communities have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk to have children with a recessive genetic disorder.