Glycogen storage disease type I (von Gierke disease)

Genetics

-Genes: G6PC (Glucose-6-phosphatse; GSDIa; 80%; 17q21.31); SLC37A4 (Glucose-6-phosphate exchanger; GSDIb; 20%; 1q23.3)

-AR

Clinical findings/Dysmorphic features

-GSDIa and GSDIb are clinically indistinguishable

-Accumulation of glycogen and fat in liver and kidneys --> hepatomegaly and renomegaly

-Untreated infants present at 3-4mths: hepatomegaly, lactic acidosis, hyperuricemia, hyperlipidemia, hypertriglyceridemia, and/or hypoglycemic seizures

-Children: doll-like faces with fat cheeks, thin extremities, short stature, protuberant abdomen

-Xanthoma (fatty growths develop underneath the skin) and diarrhea may be present

-Impaired platelet function can lead to a bleeding tendency with frequent epistaxis

-Untreated GSDIb: impaired neutrophil and monocyte function, chronic neutropenia, IBD --> recurrent bacterial infections, oral and intestinal mucosal ulcers

-Long-term complications: growth retardation, osteoporosis, delayed puberty, gout, renal disease, pulmonary hypertension, hepatic adenomas with potential for malignant transformation, polycystic ovaries, pancreatitis, changes in brain function

-Normal growth and puberty in treated children; most affected individuals live into adulthood

Etiology

-Incidence of GSDI is 1 in 100,000 individuals

Pathogenesis

-GSDs: abnormalities in enzymes/transporters in glycogen synthesis and degradation

-Glucose is stored as glycogen: glucose is phosphorylated to glucose-6-phosphate --> Glucose-6-phosphate is converted to glucose-1-phosphate --> Glycogen synthase catalyzes formation of α-1,4-linkages --> every 10 glucose, a branching enzyme forms an α-1,6-linkage

-lack of G6Pase catalytic activity or glucose-6-phosphate exchanger SLC37A4 activity in liver --> inadequate conversion of glucose-6-phosphate into glucose through normal glycogenolysis and gluconeogenesis pathways causes:

1) severe hypoglycemia

2) high lactate (due to increased glycolysis)

3) high uric acid (glucose-6-phosphate is shunted into the pentose phosphate shunt)

4) high triglycerides (increased synthesis of acetyl CoA)

Genetic testing/diagnosis

-Hypoglycemia: fasting blood glucose <60 mg/dL (nl 70-120 mg/dL); lactic acidosis: blood lactate >2.5 mmol/L (nl 0.5-2.2 mmol/L); hyperuricemia: blood uric acid >5.0 mg/dL (nl 2.0-5.0 mg/dL); hyperlipidemia: triglycerides >250 mg/dL (nl 150-200 mg/dL) (hypertriglyceridemia causes the plasma to appear "milky"); cholesterol >200 mg/dL (nl 100-200 mg/dL)

-Diagnosis: Biallelic mut in G6PC (GSDIa)/SLC37A4 (GSDIb) or deficient hepatic enzyme activity

-G6PC and SCL37A4: Seq 95%, InDel: rare; targeted: G6PC, p.Arg83Cys in AJ, p.Gln347X in Amish

Others

-SLC37A4 brings G6P to inner ER membrane where G6Pase enzyme is located

-Symptoms appear around 3/4 months --> sleep through night and do not eat as frequently

-6-month-old boy presents with hepatomegaly, renomegaly, hypoglycemia and lactic acidosis

-G6P expressed only in liver: prior to isolation of gene, prenatal diagnosis was not possible