Carbohydrate Metabolism Disorders

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Disclosures: None
PI initiated Clinical trial in GSD1 sponsored by Ultragenyx
Outline of Topics to Cover

• Glycogen Storage Disorders
• Glycolysis (include PDH)
• Gluconeogenesis (include PC)
• Fructose/Galactose Metabolism
• Pentose Phosphate/TALDO
CHO metabolism
Glycogen Storage disease

• Overview of Glycogen metabolism
• Types of Hepatic glycogen storage disorders
• Clinical Presentation
• Diagnosis
• Management
• New perspectives and therapy
• Muscle GSDs- birds eye view
Sources of Blood Glucose

a) Diet is not always reliable

b) **Glycogenolysis**: Glycogen breakdown providing a rapidly available supply of glucose

c) **Gluconeogenesis**: limited slow supply of glucose in response to low glucose levels.
Glucose utilization

- **Stage 1** – post-prandial
  - All tissues utilize glucose
- **Stage 2** – post-absorptive
  - Maintain blood glucose
  - Glycogenolysis
  - Glucogenogenesis
  - Lactate
  - Pyruvate
  - Glycerol
  - Amino acids
  - Propionate
  - Spare glucose by metabolizing fat

- **Stage 3** – Early starvation
  - Gluconeogenesis

- **Stage 4** – Intermediate starvation
  - Gluconeogenesis
  - Ketone bodies

- **Stage 5** – Starvation
  - Ketones mainly

Normal Glycogen metabolism

- Early fasting, endogenous glucose is generated by glycogenolysis
- Glycogen (liver) is converted to G6P under regulation of debranching enzyme, hepatic glycogen phosphorylase, and phosphorylase kinase.
- Prolonged fasting, glucose is generated by gluconeogenesis from amino acids, lactate, glycerol
- Both processes generate G6P which must be dephosphorylated to transport glucose out of the cell
- **The enzyme responsible for this is G6Pase**
- **GSD** is a group of inherited disorders characterized by deposition of an abnormal quantity or form of glycogen in the tissues.
  - Enzyme may be defective in a single tissue (e.g. liver)
  - Or more generalized e.g. muscle, kidney, intestine
Glycogen storage disorders types

**Predominately Hepatic:** hypoglycemia, hepatomegaly, growth retardation
- GSD 0 – glycogen synthase
- GSD I – glucose-6-phosphatase or transport systems in ER
- GSD III – debranching enzyme *
- GSD IV – branching enzyme *
- GSD VI – liver phosphorylase *
- GSD IX – liver phosphorylase b kinase *
- GLUT2- aka Fanconi Bickel syndrome- formerly known as GSDXI Is a glucose utilization disorder ( not a GSD). GSDXI is currently known as

**Predominately Muscle:** exercise intolerance , muscle cramps, rhabdomyolysis
- GSD II – acid alpha-glucosidase- Pompe disease
- GSD V – muscle phosphorylase- McArdle disease
- GSD VII - muscle phosphofructokinase- Tauri disease
Glycogen storage disorders

http://www.mghlysosomal.org/Pompe.html
Glycogen storage disease type 1 (GSD1)

- Incidence: 1:100,000 births
- Approx. 25% of all GSDs diagnosed
- GSD1a (80%)- due to glucose-6-phosphatase enzyme complex deficiency
- GSD1b (20%)- due to G6Pase translocase deficiency
- Mutations/ deficiency leads to impaired glycogenolysis and gluconeogenesis
GSD1

- Inability to release free glucose from glucose-6 phosphate during glycogenolysis.
- Severe hypoglycemia $\Rightarrow$ convulsions $\Rightarrow$ coma (especially children).
- Glucagon is increased (but ineffective)
- Insulin is low until fed,
- Ketosis is not common.
- High concentrations of G6P generated are shunted into alternative pathways causing hyperlactatemia, hyperlipidemia, hyperuricemia
Biochemical findings GSD1

- **Elevated lactate** due to shunting down glycolytic pathway resulting in lactic acidosis, high pyruvate, and alanine.

- **Hyperlipidemia** due to ↑↑ synthesis of TGs from shunting to acetyl CoA, ↓↓ CPT 1 by Malonyl CoA, and decreased lipid serum clearance.

- **Hyperuricemia** due to shunting of G6P into the pentose phosphate pathway and ↑ degradation of adenine nucleotides result in ↑ uric acid production. Competitive inhibition of uric acid excretion by lactate results in decreased renal clearance.
GSD1: Clinical Features

- Growth retardation and delayed puberty.
- Fat accumulation: in cheeks, buttocks, doll face appearance
- Abdominal distention: due to hepatomegaly
- Hepatomegaly and nephromegaly due to glycogen storage in both organs.
- Anorexia, weight loss, vomiting
- Muscles flabby, poorly developed
- Bleeding tendency - nose bleeds, easy bruising due to acquired vWD, and platelet aggregation defects
Additional clinical features in GSD1b

• ~1/5 of GSD1 cases- similar features to GSD1a plus
  • Neutropenia
  • Neutrophil dysfunction (impaired motility and migration
  • Frequent and severe infections which can affect upper and lower respiratory tract, the skin, genital and urinary tract
  • Deep abscess (Brain)
  • Peri-oral and peri-anal infections
  • Protracted diarrhea and inflammatory bowel disease (pseudo Crohn disease)
  • ? Risk of autoimmune disease e.g. hypothyroidism
Complications of GSD1
Adolescent and Adult manifestations

- Dietary treatment improved survival and quality for GSDI patients but defect remains
- Nephropathy - nephromegaly with hyperfiltration - proteinuria, RTA with renal Fanconi syndrome, renal stones (Uric A and Ca oxalates)
- Hepatic adenoma, hepatocellular carcinoma
- Osteoporosis
- Chronic Anemia, iron deficiency anemia
- Pulmonary hypertension
- Acute pancreatitis (high TGs)
- Polycystic ovaries
- Gout
Diagnostic and follow up workup for GSD1

- During hypoglycemia: exclude insulin, cortisol, GH and FFA
- Check serum FFA/ beta hydroxybutyrate
- Check lactate, uric acid, and TGs (metabolic control parameters) besides liver functions, electrolytes
- Check CBC with diff (neutropenia) GSD1b
- Iron level, TIBC, Ferritin, Vitamin D yearly
- Urine micro albumin/ creatinine random
- Urine amino acids, electrolytes, phosphorus (RTA)
- Liver U/S children, MRI or CT (adults) or if there is adenoma
- GSD1b- inflammation markers eg CRP- GI studies
Treatment

- **Frequent feeding**
  - Provide a constant source of CHO sufficient to maintain blood glucose levels.

- **Newborns and infants:**
  - Frequent meals and continuous nocturnal feeding via a nasogastric tube or glucose infusion (during fasting) to maintain an appropriate glucose infusion rate (GIR).
  - Newborns: 8–10 mg of glucose/kg/min, infants and young children: 5–7 mg/kg/min
  - Older children and Adults: 4-6 mg/kg/min

- An ER letter is provided for emergencies
- Medical bracelet alert for risk of hypoglycemia is recommended.
Diet guidelines

- Small, frequent feedings high in complex carbohydrates evenly spaced over 24 hours.
  - 60 – 70% Carbohydrates
  - 10 – 15% Protein (RDA)
  - Remainder from Fat (<30%)
- Ekvall, 2005; ESGSD I, 2003; Goldberg, Slonim, 1993

Diet Restrictions

- Simple sugars as Fructose and Galactose are metabolized to glucose-6-phosphate and thus are limited/avoided in the diet
  - No sucrose (sugar) = fructose + glucose
  - No fructose (fruit, juice, HFCS)
  - Limited lactose (dairy) = galactose + glucose

- Restrictions are variable from center to center and patient to patient
- Restrictions made to decrease lactate production, and prevent insulin peaks.
Diet for infants

- Feed every 2 – 3 hours during the day
- Choose a sucrose-free, lactose-free formula Nutramigen, Prosobee (soy)

- OGF therapy overnight (4 – 6 mg glu /kg/min)
  - 8 – 9 mg/kg/min (Schwenk, 1986); Yields BG 90 mg/dl
  - Blood Glucose monitoring

- Introduce baby food at 4 – 6 months
  - Advance in a timely manner
  - Emphasize complex carbs
    - Oatmeal, barley, rice, pastas, legumes
    - Maintain normal BG better than potatoes and bread
Uncooked cornstarch

- **Age of introduction – 1 year of age** (when pancreas is mature amylase is fully functional)
- May try earlier at 10 mo, start low and go up slow), as **side effects may occur**
  - Gas, bloating, diarrhea – may be transient
  - May be worse in GSD type Ib (IBD, malabsorption)
  - Gradual introduction may reduce side effects
  - Pancrealipase (lipase, protease, amylase) can be used in conjunction with cornstarch therapy to reduce side effects
Dosing of Cornstarch

- 1.5 g CS/kg BW (IBW) every 3-4 hours in young children
- 1.7 – 2.5 g CS/kg BW (IBW) every 6 – 8 hours in older children, adolescence and adults
- For adult: OGF: 4 – 6 mg glu/kg/min (adjust based on BG)
- Individualized; based on BG levels; smaller more frequent doses given in between meals may give best control.
- Avoid heat, ascorbic acid and lemonade
  
  Sidbury, 1986; Visser, 2002

- Don’t give it with citrate (bicitra), space it from it as it limits absorption of cornstarch

**BW (IBW): body weight/ideal body wt**
Modified cornstarch: Glycosade

- Characteristics of the conventional and Glycosade examined in the study

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Glycosade</th>
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<tbody>
<tr>
<td>Moisture content (%)</td>
<td>10.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Amylopectin content (%)</td>
<td>72.8</td>
<td>99.5</td>
</tr>
<tr>
<td>Total carbohydrate (%)</td>
<td>87.5</td>
<td>82.5</td>
</tr>
<tr>
<td>Resistant starch (%)</td>
<td>60.5</td>
<td>67.7</td>
</tr>
<tr>
<td>Glycemic index (GI units)</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>

- Conventional corn starch was Argo (ACH Food Companies Inc, Memphis, TN); experimental starch was Glycosade (Vitaflo International Ltd, Liverpool, United Kingdom).

- Randomized, 2-d, double blinded, crossover pilot study (12 subjects, GSD Ia and Ib, >13 years)

Summary of the Results

- Glycosade maintained BG longer than Argo
- Argo demonstrated a higher peak glucose concentration and a more rapid rate of fall

Other treatments for GSD1

- Multivitamin/mineral supplement, including Iron, Calcium and Vitamin D supplementation and follow up labs.
- Allopurinol for hyperuricemia/ gout
- GCSF for patients with GSD1b and neutropenia.
- Citrate in patients with stones or RTA space away from cornstarch
- ACEI or ARBS for renal hyper-filtration- microalbuminuria
- Liver transplant +/- kidney transplant

**Indications:** hepatic adenomas, or carcinoma, poor metabolic control with lack of compliance, renal failure
New Therapy for GSD1b

- Repurposing empagliflozin for Tx GSD1b

Clinical Trials GSD I

• Long-Term Follow-up to Evaluate the Safety and Efficacy of Adeno Associated Virus (AAV) Serotype 8 (AAV8)-Mediated Gene Transfer of Glucose-6-Phosphatase (G6Pase) in Adults With Glycogen Storage Disease Type Ia (GSDIa)

• Anaplerotic Therapy Using Triheptanoin for Patients With Glycogen Storage Disease Type I

• Safety, Efficacy Evaluation of Empagliflozin Administration for Neutropenia in Glycogenosis Type 1b and G6PC3 Deficiency

• Glycogen Storage Disease Breath Test Study

• Endogenous Glucose Production in Patients With Glycogen Storage Disease Type Ia
Hepatic GSDs - ketotic hypoglycemia

- **Glycogenolysis disorders: Gluconeogenesis remains intact**
  - GSD type 0 (glycogen synthase deficiency)
  - GSD type 3 (amylo-1,6-glucosidase deficiency)
  - GSD type 6 (liver glycogen phosphorylase deficiency)
  - GSD type 9 (phosphorylase kinase deficiency)

- **Glucose utilization defect:**
  - Fanconi Bickel syndrome (GLUT2 mutation)
    (formerly known as GSD type XI)
GSD type 3- Cori disease

- Debranching enzyme (amylo-1,6-glucosidase) is deficient.
- Inability to remove glucose in alpha 1,6 linkages
- Hypoglycemia milder than GSD 1 (intact gluconeogenesis)
- Fasting ketotic hypoglycemia, postprandial hyperlactatemia
- Growth may be retarded.
- GSD3a have liver and muscle± heart disease
- GSD3 b is predominantly liver disease- w/o muscle disease
- Hepatomegaly early in life (3-6m), with elevated liver enzymes.
- hepatic fibrosis, cirrhosis and liver damage may occur later in life.
- Muscle weakness with myopathy and wasting later in life
- Elevation of CK
- HCM sudden death- possibly arrhythmia
Treatment of GSD 3

• Frequent feeding.

• **High protein diet:** beneficial for providing amino acids as substrate for gluconeogenesis and for muscle protein synthesis and as an alternate fuel for muscle metabolism.

• Cornstarch when indicated ( too much and too little are detrimental)

• Less carbs are better- due to abnormal structure of glycogen

• Liver transplant- due to liver cirrhosis or malignancy, cirrhosis. Curative in GSD3b ( not GSD3a)
GSD 4: ANDERSON DISEASE

- Branching enzyme deficiency.
- $\alpha$-1,4-glucan-6-glucosyl transferase is deficient.
- Inability to form glycogen branches through alpha 1,6 linkages
- Normal at birth; then FTT, Hepatomegaly and splenomegaly, portal hypertension
- Nonspecific gastrointestinal symptoms.
- Poor growth, hypotonia.
- Follows course of progressive liver cirrhosis.
- Hypoglycemia (not a feature) occurs due to liver failure
- Patients can also have muscle and heart disease (CM)
- Death: 2-4 years.
- Cause of death liver failure, and or cardiomyopathy
GSD4 Diagnosis - Treatment

- Abnormal ALT/AST, low albumin, ↑INR. Evidence of liver cirrhosis, portal hypertension
- Liver biopsy: accumulation of abnormal glycogen, long, unbranched outer chains with fewer branching points, and amylopectin-like polyglucosans.
- Hepatic fibrosis with periodic-acid Schiff-positive, diastase-resistant inclusions in hepatocytes and fibrillary inclusions characteristic of amylopectin by electron microscopy.
- Enzymatic assay revealed deficient hepatic branching enzyme activity with normal activity of glucose-6-phosphatase, debranching enzyme and phosphorylase activities.
- Treatment: decrease CHO, protein may need to be restricted due to liver failure
- Only treatment liver transplant ± heart transplant
GSD6- HERS DISEASE

- Due to Liver phosphorylase deficiency. Gene defect PYGL on chromosome 14q21-q22 (AR)

- Symptoms
  - Isolated Hepatomegaly
  - growth/motor development delay
  - mild fasting hypoglycemia and fasting ketosis
  - moderate hyperlipidemia and elevated LFTs

- Diagnosis by enzyme assay in liver biopsy specimen

- Treatment: avoid prolonged fasting

- Prognosis: most symptoms resolve at puberty

Treatment

- High protein diet.
- Frequent meals.
GSD 9a

- **Etiology:** Liver phosphorylase B-kinase deficiency
- **Gene:** PHKA2 on chromosome Xp22 (X-linked)
- **Symptoms:** As in GSD 6, but muscle involvement can occur
- **Diagnosis:** Enzyme assay in RBC, but presence of isoenzymes often requires tissue specimen
- **Treatment:** Prevention of prolonged fasting by bedtime snack
- **Prognosis:** Benign, most symptoms resolve during puberty
- **More common than GSD 6**
GSD 0

- Etiology: Deficiency of liver glycogen synthase
- Gene: GYS2 on chromosome 12p12.2
  - Ketotic hypoglycemia with normal fasting Lactate, drowsiness, fatigue, convulsions.
  - **No hepatomegaly**
  - Often postprandial hyperglycemia and hyperlactacidemia with glycosuria
  - Diagnosis: Enzyme assay requires liver biopsy. Molecular genetic analysis of GYS2
- Treatment: Symptomatic (frequent, protein-rich feedings; uncooked cornstarch at night)
- Prognosis: Good, but females at risk of hypoglycemia during pregnancy
Fanconi Bickel syndrome

- Glucose utilization defect due to hepatic/intestinal/renal glucose-galactose transporter defect (GLUT2/SLC2A2 recessive mutations)
- Presents with hepatomegaly and tubulopathy due to glucose/galactose intolerance in the fed state.
- Not classified as a Glycogenosis, it mimicks GSD type 1 and Galactosemia early in infancy.
- Clinically – hepatomegaly, hypophosphatemic rickets, failure to thrive, short stature
- Biochemical findings: renal tubular acidosis with reducing substances in urine, low K, Ca, Mg, aminoaciduria, electrolytes, mineral loses in urine+-/carnituria- low serum carnitine.
- Diagnosis: SLC2A2 Mutation testing
- Treatment: protein, galactose free diet, complex CHO, supplementation of all electrolyte, mineral losses, carnitine if low
Resources

Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

Priya S. Kishnani, MD1, Jennifer Goldstein, MS, PhD4, Stephanie L. Austin, MS, MA1, Pamela Arn, MD3, Bert Bachrach, MD4, Deeksha S. Bali, PhD1, Wendy K. Chung, MD, PhD5, Areeq El-Gharbawy, MD6, Laurie M. Brown, CCRC7, Stephen Kahler, MD8, Surekha Pendyal, MEd, RD1, Katalin M. Ross, RDN, LDN8, Laurie Tsilianidis, MD10, David A. Weinstein, MD, MMSc11 and Michael S. Watson, MS, PhD12

ACMG Practice Guidelines

Glycogen Storage Disease Type III diagnosis and management guidelines

Priya S. Kishnani, MD1, Stephanie L. Austin, MS, MA1, Jose E. Abidinur, MD2, Pamela Arn, MD3, Deeksha S. Bali, PhD1, Anne Boney, MEd, RD, LDN12, Laura E. Case, PT, DPT, MS, PCS2, Wendy K. Chung, MD, PhD5, Dev M. Desai, MD8, Areeq El-Gharbawy, MD4, Ronald Haller, MD12, G. Peter A. Smit, MD, PhD5, Alastair D. Smith, MB, ChB12, Lisa D. Hobson-Webb, MD12, Stephanie Burns Wechsler, MD1, David A. Weinstein, MD, MMSc11, Joseph I. Wolfsdorf, MB, BCh12 and Michael S. Watson, MS, PhD12
GSD II: Pompe disease

- Due to lysosomal $\alpha$-glucosidase deficiency
- 3 clinical forms: age of onset/ severity correlates with the level of residual $\alpha$-glucosidase activity and the extent of lysosomal storage of glycogen.

1. **Infantile form**:
   - Profound hypotonia (muscle weakness)
   - Macroglossia
   - Heart is strikingly enlarged: abnormal ECG.
   - Cardiac failure within the first year: 2 months - 5.5 months.
   - Respiratory difficulties.
   - Glycogen is increased in heart, muscle, liver, and kidney.
2. **Early childhood form:**
   - Progress much more slowly than the infantile form.
   - Skeletal muscle weakness.
   - Death in early childhood due to respiratory failure.
   - No patients survived beyond 19 years of age.

3. **Adult form:**
   - Myopathy with diaphragmatic weakness and respiratory distress
   - Disease slowly progresses
   - Phenotype is evolving smooth muscles- affected swallowing troubles, bladder, GI
   - Vascular- complications have been described brain, aorta.
Diagnosis and Treatment Pompe

- Echo: HCM, EKG short PR interval, wide QRS complex hypertrophy, abnormal
- CPK elevation, Hex 4?
- Acid alpha glucosidase activity in DBS
- DNA testing for mutations
- Treatment: supportive for heart failure
- ERT: Myozyme- Lumizyme
- Increased protein intake in the adult form
GSD V McArdle disease

Etiology: Myophosphorylase deficiency-

Inability to remove glucose-1 phosphate from muscle glycogen

Myoglobinuria triggered by vigorous exercise

Elevated CPK, with risk of rhabdomyolysis and renal failure.

“Second-wind” phenomenon – ability to resume moderate exercise after resting

Abnormal forearm ischemic exercise test – no rise in lactate, sometimes cramping. Elevated CK

Diagnosis: mutation analysis 3 common mutations detect >80% of McArdle disease in a population of European descent

Enzyme activity: Glycogen phosphorylase deficiency in flash-frozen muscle (and elevated glycogen content)

Treatment: CHO/sucrose at the time of exercise
GSDVII Tarui disease

• Muscle phosphofructokinase deficiency

• Inability to transform fructose-6 phosphate into fructose-1,6 biphosphate in muscle

• Compensated hemolytic anemia (RBC defect)

• Exercise-induced rhabdomyolysis

• Progressive myopathic pain/exercise intolerance

• **Out of wind phenomena** - due to inhibition of FAO.

• Treatment of PFK no known specific treatment

• Avoid simple sugars and glucose

• normal saline, not glucose containing fluids.
Effect of CHO/sugar reduction in GSDVII
GSD14

Clinical
GSD14, also known as phosphoglucomutase-1 deficiency or congenital disorder of glycosylation type I, has a wide clinical spectrum with predominantly milder myopathy form or severe form with multisystem involvement and congenital anomalies (86).

Metabolic findings and diagnosis
Diagnostic confirmation requires molecular analysis of the PGM1 gene.

Treatment
In a small study, supplementation with up to 1.5 g/kg/day of oral D-galactose showed improvement or normalization of liver function, coagulation profile and transferrin profile (86).
<table>
<thead>
<tr>
<th>GSD type/name (phenotype MIM number)</th>
<th>Enzyme defect</th>
<th>Gene defect (OMIM number)</th>
<th>Chromosome location</th>
<th>Inheritance</th>
<th>Incidence</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD0A/Liver GSD 0 (240600)</td>
<td>Liver glycogen synthase</td>
<td>GYS2 (138571)</td>
<td>12p12.1</td>
<td>AR</td>
<td>Unknown (&lt;30 cases reported)</td>
<td>Fasting Ketotic hypoglycemia; hyperketonemia; hypoglycemic seizures; post-prandial hyperglycemia; post-prandial hyperlactatemia</td>
</tr>
<tr>
<td>GSD0B/Muscle GSD 0 (611556)</td>
<td>Muscle glycogen synthase</td>
<td>GYS1 (138570)</td>
<td>19q13.33</td>
<td>AR</td>
<td>Unknown (10 cases reported)</td>
<td>Muscle fatigue; seizures (rare); risk of cardiac arrest in childhood</td>
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<td>GSD1A/Von Gierke/ Hепatorenal (232200)</td>
<td>Glucose-6-phosphatase</td>
<td>G6PC (613742)</td>
<td>17q21.31</td>
<td>AR</td>
<td>1 in 20,000 (Ashkenazi Jewish population)–1 in 100,000</td>
<td>Fasting hypoglycemia; lactic acidosis; hepatomegaly; growth delay/short stature; doll-like facies; elevated liver enzymes; renal dysfunction; hyperuricemia; hypertriglyceridemia; osteoporosis; anemia; hepatic adenoma; hepatocellular carcinoma</td>
</tr>
<tr>
<td>GSD1B/G6P transport defect (232220)</td>
<td>Glucose-6-phosphate translocase</td>
<td>SLC37A4 (602671)</td>
<td>11q23.3</td>
<td>AR</td>
<td>Unknown</td>
<td>Recurrent bacterial infections; neutropenia; inflammatory bowel disease; oral/intestinal mucosal ulcers; fasting hypoglycemia; lactic acidosis; hepatomegaly; doll-like facies; anemia; growth delay/short stature; hyperlipidemia; xanthomas</td>
</tr>
<tr>
<td>GSD2/Pompe/Cardiac GSD (223200)</td>
<td>Acid maltase [alpha-1,4-glucosidase]</td>
<td>GAA (606000)</td>
<td>17q25.3</td>
<td>AR</td>
<td>1 in 6,684–1 in 40,000</td>
<td>Cardiomyopathy; muscular hypotonia; enlarged tongue; respiratory failure due to muscle weakness; adult onset limb girdle dystrophy</td>
</tr>
<tr>
<td>GSD3/Forbes/Cori/Illb (210860)</td>
<td>Glycogen debrancher [amylo-1,6 glucosidase]</td>
<td>AGL (610860)</td>
<td>1p21.2</td>
<td>AR</td>
<td>1 in 100,000</td>
<td>Hepatomegaly; hypoglycemia; fasting ketosis; failure to thrive; growth delay/short stature; myopathy; hypertrophic cardiomyopathy; doll-like facies; hyperlipidemia; elevated liver enzymes</td>
</tr>
<tr>
<td>GSD4/Anderson/ Amylopectinosis/ Neuromuscular/ Polyglucosan (232500)</td>
<td>Glycogen brancher [amylo(1,4 to 1.6) transglucosidase]</td>
<td>GBE1 (607839)</td>
<td>3p12.2</td>
<td>AR</td>
<td>1 in 600,000–1 in 800,000</td>
<td>Failure to thrive; hepatoplenomegaly; progressive liver cirrhosis; fetal akinesia deformation sequence (FADS); hypotonia; muscle wasting/myopathy; cardiomyopathy; neurogenic bladder; peripheral neuropathy; leukodystrophy; cognitive impairment</td>
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<tr>
<td>GSD5/McArdle (232600)</td>
<td>Myophosphorylase</td>
<td>PYGM (608455)</td>
<td>11q13.1</td>
<td>AR</td>
<td>1 in 100,000–1 in 167,000</td>
<td>Skeletal muscle weakness; exercise-induced muscle cramping; rhabdomyolysis; myoglobinuria; “second wind” phenomenon</td>
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<tr>
<td>GSD6/Hers (232700)</td>
<td>Liver glycogen phosphorylase</td>
<td>PYGL (613741)</td>
<td>14q22.1</td>
<td>AR</td>
<td>1 in 1,000 (Mennonite population)–1 in 100,000</td>
<td>Hepatomegaly; growth retardation; mild hypoglycemia; fasting Ketotic hypoglycemia; fatigue; muscle hypotonia; motor developmental delay; osteoporosis</td>
</tr>
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Table 1 (continued)
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<tbody>
<tr>
<td>GSD7/Tarui (232800)</td>
<td>Muscle phosphofructokinase</td>
<td>PFKM (610681)</td>
<td>12q13.11</td>
<td>AR</td>
<td>Unknown, but more prevalent among Ashkenazi Jewish population</td>
<td>Hemolytic anemia; muscle weakness; exercise-induced muscle cramping; exertional myopathy; gout/hyperuricemia</td>
</tr>
<tr>
<td>GSD9A1/XLG1/formerly GSD8 (306000)</td>
<td>Alpha-2 subunit of liver phosphorylase kinase</td>
<td>PHKA2 (500798)</td>
<td>Xp22.13</td>
<td>XLR</td>
<td>Unknown (~50 cases reported)</td>
<td>Hepatomegaly; growth retardation; motor developmental delay; hypercholesterolemia; hypertriglyceridemia; elevated liver enzymes; fasting hyperketosis</td>
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<tr>
<td>GSD9B/GSD IXb (261750)</td>
<td>Beta subunit of liver and muscle phosphorylase kinase</td>
<td>PHKB (172490)</td>
<td>16q12.1</td>
<td>AR</td>
<td>1 in 100,000</td>
<td>Short stature; hepatomegaly; diarrhea; muscle weakness; hypotonia</td>
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<tr>
<td>GSD9C/GSD IXc (613027)</td>
<td>Hepatic and testis isoform— gamma subunit of phosphorylase kinase</td>
<td>PHKG2 (172471)</td>
<td>16p11.2</td>
<td>AR</td>
<td>1 in 100,000</td>
<td>Growth retardation; hepatomegaly; hypotonia; cognitive delay</td>
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<tr>
<td>GSD9D/GSD IXd (300559)</td>
<td>Alpha subunit of muscle phosphorylase kinase</td>
<td>PHKA1 (511870)</td>
<td>Xq13.1</td>
<td>XLR</td>
<td>Unknown (only 7 cases reported)</td>
<td>Muscle weakness; exercise-induced muscle pain &amp; stiffness; muscle atrophy; variable age onset, adults</td>
</tr>
<tr>
<td>GSD10/GSD X/PGAMM deficiency (261670)</td>
<td>Muscle phosphoglycerate mutase</td>
<td>PGAM2 (612931)</td>
<td>7p13</td>
<td>AR</td>
<td>Unknown (only 15 cases reported)</td>
<td>Exercise-induced muscle cramps &amp; pain; exercise intolerance; rhabdomyolysis; myoglobinuria; hyperuricemia/gout; coronary arteriosclerosis; childhood or adolescence onset</td>
</tr>
<tr>
<td>GSD11/GSD XI/LDH deficiency (612933)</td>
<td>Lactate dehydrogenase A</td>
<td>LDHA (150000)</td>
<td>11p15.1</td>
<td>AR</td>
<td>Unknown (only 12 cases reported)</td>
<td>Exercise-induced muscle cramps &amp; pain; rhabdomyolysis; myoglobinuria; uterine muscle stiffness during pregnancy; psoriatic skin lesions; onset in childhood</td>
</tr>
<tr>
<td>GSD12/GSD XII/Aldolase deficiency (611881)</td>
<td>Fructose-1,6-bisphosphate aldolase A in red cell</td>
<td>ALDOA (103850)</td>
<td>16p11.2</td>
<td>AR</td>
<td>Unknown (~10 cases reported)</td>
<td>Short stature; myopathy; mental retardation; delayed puberty; hemolytic anemia; dysmorphic facies; hepatosplenomegaly; rhabdomyolysis with febrile illness</td>
</tr>
<tr>
<td>GSD13/GSD XIII/Enolase 3 deficiency (612932)</td>
<td>Beta-enolase</td>
<td>ENO3 (131370)</td>
<td>17p13.2</td>
<td>AR</td>
<td>Unknown (only 3 cases reported)</td>
<td>Exercise intolerance; myalgia; rhabdomyolysis</td>
</tr>
<tr>
<td>GSD type/name (phenotype MIM number)</td>
<td>Enzyme defect</td>
<td>Gene defect (OMM number)</td>
<td>Chromosome location</td>
<td>Inheritance</td>
<td>Incidence</td>
<td>Clinical features</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------</td>
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<td>-------------</td>
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<td>------------------</td>
</tr>
<tr>
<td>GSD14/GSD XV/CDG11/PGM1 deficiency (614921)</td>
<td>Phosphoglucomutase-1</td>
<td>PGM1 (171900)</td>
<td>1p31.3</td>
<td>AR</td>
<td>Unknown (only 22 cases reported)</td>
<td>Short stature; cleft palate; bifid uvula; Pierre Robin sequence; hepatopathy/chronic hepatitis; intermittent hypoglycemia; dilated cardiomyopathy; exercise intolerance; muscle weakness; rhabdomyolysis; hypogonadotrophic hypogonadism; susceptibility to malignant hypothermia; hepatopathy/chronic hepatitis; intermittent hypoglycemia; variable phenotype</td>
</tr>
<tr>
<td>GSD15/GSD XV/GY1G1 deficiency (613507)</td>
<td>Glycogenin-1</td>
<td>GY1 (603942)</td>
<td>3q24</td>
<td>AR</td>
<td>Unknown (less than 20 cases reported)</td>
<td>Cardiac arrhythmias; muscle weakness</td>
</tr>
<tr>
<td>Fanconi-Bickel syndrome/previously GSD XI (227810)</td>
<td>None (glucose transport defect)</td>
<td>GLUT2/SLC2A2 (138160)</td>
<td>3q26.2</td>
<td>AR</td>
<td>Unknown (200 cases reported)</td>
<td>Tubular nephropathy; hepatorenal glycogen storage; failure to thrive; polyuria; rickets; hyperammonemia; hyperlipidaemia; ketogenic hypoglycemia; hepatosplenomegaly</td>
</tr>
<tr>
<td>GSD Heart, lethal congenital (261740)</td>
<td>Gamma-2 subunit of AMP-activated protein kinase/cardiac muscle phosphorylase kinase</td>
<td>PRKAG2 (602743)</td>
<td>7q36.1</td>
<td>AD</td>
<td>Unknown (193 cases reported)</td>
<td>Hypoglycemia; heart failure; failure to thrive; cardiomegaly; cardiomyopathy; renomegaly; WPW syndrome; fatal in early infancy</td>
</tr>
<tr>
<td>Danon disease/lysosomal-associated membrane protein-2 deficiency/formerly GSD2b or GSD IIb (300257)</td>
<td>[lysosomal-associated membrane protein-2 def-cy]</td>
<td>LAMP2 (300606)</td>
<td>Xq24</td>
<td>XLD</td>
<td>Unknown (171 cases reported)</td>
<td>Cardiomyopathy; skeletal myopathy; WPW syndrome; intellectual disability; hepatomegaly; retinopathy; arrhythmia</td>
</tr>
<tr>
<td>Brain GSD/Lafordin deficiency (254780)</td>
<td>Lafordin; E3 ligase</td>
<td>EPN2A (607566); NHURC1/EPM2B (608072)</td>
<td>6q24.3; 6p22.3</td>
<td>AR; AR</td>
<td>Unknown; unknown</td>
<td>Epilepsy; hallucinations; dementia</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; XLD-X-linked dominant, XLR-X-linked recessive.
Pyruvate Dehydrogenase: rate limiting step for glycolysis

The PDH complex contains 3 enzymes

**E1 = Pyruvate dehydrogenase** (an $\alpha_2\beta_2$ heterotetramer) PDH: irreversible oxidative decarboxylation of pyruvate to acetyl-Co. Precedes entry of glucose carbon into the TCA cycle. Fundamental for aerobic glycolysis esp. in the brain where it is the obligatory pathway for energy generation under normal conditions. The **most common form is caused by mutations in the X-linked E1 alpha gene**; other causes are due to alterations in recessive genes.

**E2 = Dihydrolipoyl transacetylase** forms the structural core and accepts acetyl groups from E1 and transfers them to coenzyme A

**E3 = Dihydrolipoyl dehydrogenase** also active in the branched-chain ketoacid dehydrogenase and alpha-ketoglutarate dehydrogenase complexes

**E3 binding protein (protein X)** involved in the interaction between the E2 and E3 subunits

Requires 5 different prosthetic groups and coenzymes:

1- **Thiamine pyrophosphate (TPP)**
2- **Flavin adenine dinucleotide (FAD)**
3- **Lipoic acid**
4- **Coenzyme A (CoA)**
5- **Nicotinamide adenine dinucleotide (NAD)**
PDHD: Broad clinical spectrum: E1a subunit is X-linked, Xp22. Thiamin cofactor interacts with this subunit. Most commonly mutated in PDH deficiency. Symptoms in females often approximate males. Neonatal onset, Infantile form, Late onset adults

- Nonspecific symptoms (triggered by stress, fever, illness, high carbohydrate intake)
  - Severe lethargy, poor feeding, tachypnea
  - Seizures
  - Gray matter degeneration with foci of necrosis and capillary proliferation in the brainstem/subacute necrotizing encephalopathy (Leigh syndrome), agenesis of the corpus callosum
  - Severe hypotonia, weakness, spasticity
  - Dysmorphic features: Microcephaly with narrow head, thin upper lip, wide nasal bridge, long philtrum (fetal alcohol facies)

- Developmental nonspecific signs
  - Mental delays
  - Psychomotor delays
  - Growth retardation
Late onset PDH deficiency

• Consider when unexplained, recurrent, acute neurologic symptoms
• Recurrent episodes of Carbohydrate sensitive
• Ataxia, Peripheral neuropathy, dystonia
• Episodic peripheral weakness
• Complex extrapyramidal disorders, recurrent dystonia
• Blood and CSF lactate may be normal
• Cognition may be normal
• Treatment: reduction of carbohydrates, thiamin, ketogenic diet
E2 deficiency

- Mutations in the *DLAT* gene (11q23.1) encoding the dihydrolipoamide acetyl transferase E2 subunit of the PDH complex
- AR, consanguinity is commonly reported.
- **Clinical manifestations**
  - Extremely Rare 4 cases?
  - Present later in childhood with movement disorders
  - Lesions in the globus pallidus looks like pantothenate kinase-associated neurodegeneration (PKAN).
- **Generalized hypotonia**
  - Delayed psychomotor development.
  - Lactate concentration may be normal in both blood and cerebrospinal fluid.
  - Hyperammonemia and nonspecific amino acid elevation are associated with E2 enzyme deficiency, which is more common during acute illnesses.
- Treatment may respond to Lipoic acid and thiamin and or ketogenic diet.
E3 deficiency

• Shared with two other enzymes
  • α-ketoglutarate dehydrogenase
  • Branched chain ketoacid dehydrogenase (MSUD)

• Clinical features
  • Typically Leigh syndrome
  • Milder variants described
  • Don’t respond well to treatment
Lab values

Confirmation of Diagnosis: Mutation testing, del-dup, enzyme testing in fibroblasts

• Lactate and Pyruvate elevated in blood and cerebrospinal fluid lactate/pyruvate ratio is low

• Lactate-to-pyruvate ratio is only diagnostically useful to differentiate pyruvate dehydrogenase complex deficiency from other forms of congenital lactic acidosis at higher lactate levels (>5 mmol/L).

• Elevated serum alanine levels

• E2 deficiency, high non specific serum AAs and hyperammonemia

• If E3 deficient, high BCAA, αKG in serum and urine

• Lactic acidosis

• Elevated branched-chain amino acids

• MSUD- like metabolites in urine organic acids
Treatment (general)

- Cofactor supplementation with thiamine, ketogenic diet, carnitine, and lipoic acid is the conventional therapy.
- Thiamine-responsive cases rare - children who are diagnosed at older than 1 year, high-dose thiamine (400 mg/day).
- Ketogenic diets (with restricted carbohydrate intake) have been used to control lactic acidosis.
- Dichloroacetate reduces the inhibitory phosphorylation of PDC. Resolution of lactic acidosis is observed in patients with E1 alpha enzyme subunit mutations that reduce enzyme stability.
- Oral dichloroacetate administered for 6 months was found to be well tolerated and blunted the postprandial increase in circulating lactate but did not improve neurologic or other clinical measures. *Pediatrics*. 2006 May. 117(5):1519-31.
- Long-term use is associated with reversible peripheral neuropathy and elevation in liver transaminases.
- Co-administration of thiamine appears to protect against neuropathy in animals.
- Because of the largely unknown benefit of this compound, it remains an investigational drug.
- Oral citrate is often used to treat acidosis.
Pyruvate Carboxylase: 1\textsuperscript{st} step in gluconeogenesis

- 1\textsuperscript{st} enzyme in gluconeogenesis, catalyzes pyruvate to oxaloacetate
- Other two gluconeogenic enzymes fructose-1,6-bisphosphatase and glucose-6-phosphatase.
- Essential role in
  - TCA cycle (anaplerosis)- repleting oxaloacetate
  - Gluconeogenesis
- Uses biotin as a cofactor, is tissue specific (liver, pancreas, brain, adipocytes)
- Controls fuel partitioning toward gluconeogenesis, lipogenesis and insulin secretion.
Pyruvate Carboxylase Deficiency

- **Clinical spectrum is broad** Mild to Severe: Failure to thrive, developmental delay, recurrent seizures, and metabolic acidosis. **Brain MRI.** Symmetric cystic lesions and gliosis in the cortex, basal ganglia, brain stem, or cerebellum; generalized hypomyelination; and hyperintensity of the subcortical frontoparietal white matter in Ventricular dilation, cerebrocortical and white matter atrophy, or periventricular white matter cysts.

- **Magnetic resonance spectroscopy (MRS).** Brain MRS shows high levels for lactate and choline and low levels for N-acetylaspartate. **Pathophysiology.** The glutamine-glutamate cycle in astrocytes requires a continuous supply of oxaloacetate provided by the reaction catalyzed by PC enzyme activity.

- Three clinical types are recognized:
  - Type A (infantile/North American form): most die in infancy or early childhood.
  - Type B (severe neonatal/French form): hepatomegaly, pyramidal tract signs, and abnormal movement, early death (early infancy).
  - Type C (intermittent/benign form): normal-mild delay in development and episodic metabolic acidosis during illness

Pyruvate Carboxylase Deficiency

• Biochemical findings by PC deficiency type [Wang et al 2008]
• Type A. Infantile-onset mild to moderate lactic acidemia; normal lactate-to-pyruvate ratio despite acidemia
• Type B. Increased L/P ratio >20; increased acetoacetate to 3-hydroxybutyrate ratio. PAA: increased citrulline, proline, lysine, and ammonia; low glutamine. Ammonia is high
• Type C. Episodic metabolic acidosis. PAA: normal citrulline, elevated lysine, proline
• The L/P ratio is usually normal in PC deficiency type A and C (<20).
Biochemical findings in Pyruvate Carboxylase

- Amino acid concentrations vary with the general metabolic state. In serum and urine:
  - High alanine, citrulline, and lysine; low aspartic acid and glutamine.
    - Hyperalaninemia as a result of pyruvate shunting
    - Hypercitrullinemia and hyperlysinemia due to block in the urea cycle secondary to a low aspartic acid
    - Low aspartic acid and glutamine as a result of deficiency in the oxaloacetate precursor
  - Ketonemia. 3-hydroxybutyrate and acetoacetate concentrations are increased in blood.
    - In PC deficiency type B, the ratio of acetoacetate to 3-hydroxybutyrate is increased, reflecting a low NADH-to-NAD ratio inside the mitochondria. Lack of oxaloacetate prevents the liver from oxidizing acetyl-CoA derived from pyruvate and fatty acids. The expanded acetyl-CoA pool results in hepatic ketone body synthesis [De Vivo et al 1977].
  - Hypoglycemia. Oxaloacetate deficiency limits gluconeogenesis. Important: Hypoglycemia is not a consistent finding despite PC is the first rate-limiting step in gluconeogenesis.
  - Hyperammonemia results from poor ammonia disposal and decreased urea cycle function.
  - Cerebrospinal fluid (CSF) ↑ lactate and pyruvate concentrations, ↓ glutamine, ↑ glutamic acid, proline concentrations

Molecular testing

• **Genotype-Phenotype Correlations**


  • **Type B.** Missense variants, deletions, and splice donor site pathogenic variants occur in homozygotes, compound heterozygotes, and individuals with mosaicism (see [Table 2]) [Wang et al 2008].

  • **Type C.** A heterozygous variant (p.Ser266Ala) and somatic mosaic variant (p.Ser705Ter) were observed in the first individual described [Wang et al 2008]; compound heterozygosity for the pathogenic variants p.Thr569Ala and Leu1137ValfsTer1170 was observed in the second individual described [Wang et al 2008].

• **Mosaicism** (see [Molecular Genetics]) was found in five individuals [Wang et al 2008]: Four had prolonged survival; the fifth (type B) died from unrelated medical complications.

• **Homozygous pathogenic variants.** The deaths of the more severely affected individuals with type B correlated with homozygous variants, which produced very low amounts (2% and 3%) of fibroblast PC protein [Wang et al 2008: Table 2].
Treatment: ineffective

- Alternative energy sources, hydration, and correction of the metabolic acidosis during acute decompensation. Correction of the biochemical abnormality can reverse some symptoms, but central nervous system damage progresses regardless of treatment [DiMauro & De Vivo 1999].
- Biotin to optimize residual PC enzyme activity is usually of little efficacy.
- "Anaplerotic therapy" to correct the energy deficit by providing alternative substrate for both the citric acid cycle and the electron transport chain for enhanced ATP production [Roe & Mochel 2006].
- Citrate supplementation reduces the acidosis and provides substrate for the citric acid cycle [Ahmad et al 1999].
- Aspartic acid supplementation allows the urea cycle to proceed and reduces the plasma and urine ammonia concentrations but has little effect on the neurologic disturbances as the aspartate does not enter the brain freely [Ahmad et al 1999].
- Triheptanoin, an odd-carbon triglyceride, providing a source for acetyl-CoA and anaplerotic propionyl-CoA, [Mochel et al 2005, Mochel 2017]. Triheptanoin provides C5-ketone bodies that can cross the blood-brain barrier, therefore providing substrates for the brain.
- Orthotopic liver transplantation has reversed the biochemical abnormalities in two affected individuals [Nyhan et al 2002].
Fructose Metabolism

• 3 inborn errors are known in the pathway of fructose metabolism;
• 1- Hereditary fructose intolerance
• 2- Fructose-1,6-bisphosphatase deficiency
• 3- Essential or benign fructosuria due to fructokinase deficiency;

Nutrients. 2017 Apr; 9(4): 356
Hereditary Fructose Metabolism (HFI)

- Deficiency of aldolase B, splits F-1-P into dihydroxyacetone phosphate, glyceraldehyde in liver, small intestine, proximal renal tubule.
- Triose products of aldolase B are key intermediates in glycolysis and gluconeogenesis.
- Fructose ingestion results in accumulation of F-1-P, trapping of P leading to:
  - Block of glycogenolysis and gluconeogenesis leading to hypoglycemia, lactic acidosis – through glycolysis
  - Depletion of ATP leading to increased production of uric acid, release of Mg, impaired protein synthesis, ultrastructural lesions which are responsible for hepatic and renal dysfunction.
HFI

- IV Fructose is toxic even in healthy adults- do not use to challenge!!!!
- Some carriers- if exposed to fructose> 50gms may develop hyperuricemia, gouty attacks
- Patients develop symptoms when exposed to Fructose, sucrose or sorbitol
- Vomiting, diarrhea, abdominal pain, hypoglycemia, hepatomegaly, jaundice, and renal tubular acidosis- fanconi syndrome +ve reducing substance in urine (fructose).
- Lab findings: Lactic acidosis, hyperuricemia, elevated transaminases, INR, GGT, alk
- Ultrasound: hepatomegaly, or echogenic liver, steatosis, fibrosis
- Diagnosis: Suspicion, molecular analysis of the ALDOB gene.
- If no mutation is found despite a strong clinical and nutritional history deficient (<10%) aldolase activity in liver sample will confirm the diagnosis.
- Tx- Avoid Fructose, sucrose, sorbitol in diet, other sources (medications) Prognosis: is excellent, untreated leads liver failure, renal failure
Remember!

• Patients with HFI are at risk of iron deficiency anemia- due to deficiency of Vitamin C. Check CbC, ferritin, iron studies, supplement with both iron and Vitamin C.

• Immunizations are safe- give it when patient is well, and stable

• Patients with HFI have abnormal IEF of transferrin that is reversible when under good metabolic control
Fructose-1,6-Bisphosphatase (FBPase) Deficiency

- FBPase is a key rate limiting gluconeogenesis enzyme, its deficiency prevents formation of glucose from lactate, glycerol, and gluconeogenic amino acids, as alanine.
- Tolerance to fructose in FBPase deficiency is higher than in patients with HFI, no vomiting after ingestion (fructose, sucrose, sorbitol or glycerol).
- Triggers: catabolism as fever, diarrhea, fasting, Fructose ingestion approx. 1g/kg BW. Clinically: hypoglycemia, lactic acidosis, hyperuricemia, ketosis, liver failure
- Metabolic decompensations decrease with age, adults are more tolerant of catabolic stressors, fructose intake Pregnancy is a risk factor for metabolic decompensation, due to its increased glucose requirements
FBPase deficiency

• Clinical signs are similar to glucose-6 - phosphatase deficiency.
• Neonatal hypoglycemia is a common presenting feature, associated with profound metabolic acidosis, irritability or coma, apneic spells, tachycardia, hypotonia and moderate hepatomegaly.
• Labs: ↑ Lactate, alanine, ± ketone bodies in blood and urine. TGs are high (Pseudo hyper TGs may partially represent glycerol elevation) ↑L/P ratio.
• UOA during crises: elevated glycerol (DD glycerol kinase), and glycerol 3 phosphate (GC/MS with urease pretreatment non-extraction method is preferred if missed using organic solvent extraction pretreatment)
• Diagnosis is by molecular analysis of the FBP1 gene or FBPase activity in liver samples if no mutation is found
FBPase deficiency

- **Treatment**: Prevention
- Prevent fasting, treat using IV glucose during episodes of illness
- Small amounts of fructose (≤2 g/kg/day) is tolerated, single ingestion of high doses of fructose (>1g/kg) is harmful, especially in younger children.

- **Practice Pearls**
  - Hypoglycemia in the neonatal period (especially the first 4 days) resulting from deficient glycogen stores (consider in DD GSD1)
  - Pregnancy: Home glucose monitoring and consumption of uncooked cornstarch at night. During labor, continuous glucose infusion is recommended to maintain euglycemia.
  - ↑glycerol 3-phosphate in UOA is more specific as glycerol is also elevated in glycerol kinase deficiency, or creams, oils used in diaper area
Remember!

- HFI
  - Children have strong aversion to sweets, no teeth cavities
  - FTT with chronic fructose ingestion
  - Have renal tubular dysfunction

- FBPase deficiency
  - Children do not have GI symptoms or FTT related to chronic fructose ingestion.
  - No RTA
  - Detection of glycerol, glycerol 3 phosphate in UOA

For DD full list see genereviews: https://www.ncbi.nlm.nih.gov/books/NBK550349/
Galactose Pathway disorders

• Classic galactosemia due to galactose-1-phosphate uridyltransferase (GALT) deficiency.

• Uridine diphosphate galactose 4-epimerase (GALE) deficiency exists in at least two forms. The very rare profound deficiency clinically resembles classical galactosemia. The more frequent partial deficiency is usually benign.

• Galactokinase (GALK) deficiency is extremely rare and the most insidious, since it results in the formation of nuclear cataracts without provoking symptoms of intolerance.

• Fanconi- Bickel syndrome is a congenital disorder of galactose transport due to GLUT2 deficiency (formerly known as GSD type 11)
Exogenous Lactose → Galactose → Galactose-1-Phosphate → Glucose-1-Phosphate → Glucose-6-Phosphate

Alternate Pathways:
- Galactitol* → Increased metabolic byproducts
- Galactose → Galactonate → Galactose Dehydrogenase

*accumulation results in cataracts and cerebral edema

Biosynthesis of Glucoconjugates:
- Galactoproteins
- Galactolipids
- Mucopolysaccharides

Enzymes:
- GALK
- GALT
- GALE
- Lactase
- Galactokinase
- UDP-glucose
- UDP-galactose
Classic Galactosemia

• Whenever you consider a galactose disorder, stop milk feeding first and only then seek a diagnosis!

• Classic galactosemia: life-threatening complications including feeding problems, failure to thrive, hepatocellular damage/failure and *E coli* sepsis in untreated infants.

• Early lactose-restricted diet ASAP, during the first 10 DOL leads to resolve of neonatal signs, and prevents complications of liver failure, sepsis, and neonatal death.

• Despite adequate treatment early, children remain at risk for developmental delays, speech problems (termed childhood apraxia of speech and dysarthria), and abnormalities of motor function.

• Most females with classic galactosemia manifest premature ovarian insufficiency (POI) esp if The individual is homozygous for *p.Gln188Arg*; mean erythrocyte gal-1-P is greater than 3.5 mg/dL during therapy; and recovery of 13CO2 from whole-body 13C galactose oxidation is reduced below 5% of administered 13C galactose.

https://www.ncbi.nlm.nih.gov/books/NBK1518/
Management of classic Galactosemia

- **NBS- send GALT activity, Gal-1-P (before giving PRBCs if needed), galactitol in urine; mutation testing**

- Standard of care in any newborn who is "screen-positive" is immediate dietary restriction of galactose in the diet while diagnostic testing is under way.

- If erythrocyte galactose-1-phosphate concentration is >10 mg/dL and erythrocyte GALT enzyme activity is ≤10% of control activity (i.e., the child has classic galactosemia or clinical variant galactosemia),

- Restriction of galactose intake is continued and all milk products are replaced with lactose-free formulas containing non-galactose carbohydrates
• **Genotype-Phenotype Correlations**

• Significant *genotype-phenotype correlations* have been noted [Shield et al 2000, Tyfield 2000]. Although the *GALT* genotype informs prognosis [Guerrero et al 2000, Webb et al 2003],

<table>
<thead>
<tr>
<th>Classic Galactosemia (Alias (^1))</th>
<th>Clinical Variant Galactosemia (Alias (^1))</th>
<th>Biochemical Variant Galactosemia (Alias (^1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.[Gln188Arg]+[p.Gln188Arg] (Q188R/Q188R)</td>
<td>p.[Ser135Leu]+[Ser135Leu] (S135L/S135L) (^2)</td>
<td>c.[940A&gt;G; c.-16_119delGTCA] (4bp 5' del + N314D/Q188R) (^3)</td>
</tr>
<tr>
<td>p.[Lys285Asn]+[Lys285Asn] (K285N/K285N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.[Leu195Pro]+[Leu195Pro] (L195P/L195P)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Δ5.2 kb del/ Δ5.2 kb del) (^4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.**

*GALT* Genotypes and Biochemical/Clinical Phenotypes

1. Variant designation that does not conform to current naming conventions
2. The original identification of the p.Ser135Leu pathogenic variant was exclusively in African Americans; however, it is present on occasion in infants without known African American heritage.
3. Known as "Duarte variant galactosemia" or the "Duarte D\(^2\) variant"

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**Notes:**
- \(^1\) Alias
- \(^2\) \(4bp 5' del + N314D/Q188R\)
- \(^3\) \(c.-16_119delGTCA\)
- \(^4\) \(Δ5.2 kb del\)
Nomenclature

The genetic hypergalactosemias

- **Galactokinase deficiency secondary to pathogenic variants in GALK**: cataract, increased galactose, and galactitiol. Normal GALT and gal-1-P
- **Epimerase deficiency galactosemia secondary to pathogenic variants in GALE**
  - Gal-1-P high, galactose, normal GALT
- **Severe systemic Form- liver disease**
- **RBC- peripheral- benign restricted to RBC biochemical abnormality**
- **Galactose-1-phosphate uridylyltransferase deficiency** secondary to pathogenic variants in GALT:
  - **Classic galactosemia**
    - Severe GALT enzyme deficiency with absent or barely detectable activity in erythrocytes and liver
    - Also known as G/G and carriers as G/N
  - **Clinical variant galactosemia**
    - 1%-10% residual GALT enzyme activity in erythrocytes and/or liver
  - **Biochemical variant galactosemia**
    - 15%-33% residual GALT enzyme activity in erythrocytes
    - Includes the D₂ Duarte biochemical variant state also known as G/D
Genetically Related (Allelic) Disorders

- **Duarte variant galactosemia** an example of biochemical variant galactosemia, is associated with specific pathogenic variants in *GALT*.

- The Duarte variant (D₂) has in *cis* configuration of the pathogenic *missense* variant p.Asn314Asp and a **GTCA deletion in the promoter region** (c.-119-116delGTCA) that impairs a positive regulatory domain. It is designated c.[940A>G; c.-119_116delGTCA] (see Table 3).

- The **Los Angeles (LA) variant** (D₁) has the identical p.Asn314Asp pathogenic *missense* variant as the Duarte variant but does not have the GTCA promoter deletion. Instead, it is in *cis* configuration with the missense variant p.Leu218Leu. This variant does not cause galactosemia and is associated with increased erythrocyte GALT enzyme activity [Langley et al 1997, Elsas et al 2002].

- In biochemical variant galactosemia:
  - Erythrocyte galactose-1-phosphate is usually >1 mg/dL, but may be as high as 35 mg/dL. When the individual is on a lactose-free diet, the level is <1 mg/dL.
  - Residual erythrocyte GALT enzyme activity is usually >15% and, on average, is 25% of control values.
**Pentose Phosphate Pathway** aka phosphogluconate pathway or hexose monophosphate shunt.

- A metabolic pathway that parallels Glycolysis generating NADPH, pentoses (5-carbon sugars), and ribose 5-phosphate.
- It involves glucose oxidation, in an anabolic rather than catabolic role.
- Importance: generates precursors for nucleotide synthesis, especially important for red blood cells.
- **Oxidative Role:** Irreversible.
  - Generates two NADPH, used in FA and cholesterol synthesis and for maintaining reduced glutathione inside RBCs.
- **Nonoxidative Role:** Reversible.
  - Generates intermediate molecules (ribose-5-phosphate; glyceraldehyde-3-phosphate; fructose-6-phosphate) for nucleotide synthesis and glycolysis.
Pathways connected to the PPP

- PPP is connected to two pathways of carbohydrate metabolism: glycolysis and the glucuronic acid pathway.
Pentose phosphate pathway Functions as an alternative route for glucose oxidation that does not directly consume or produce ATP.

- Produces **NADPH** for FA and cholesterol synthesis.
- Fructose-6-phosphate and glyceraldehyde-3-phosphate generated in the pathway reenter glycolysis.
- NADPH is also used to reduce glutathione (γ-glutamylcysteinylglycine).
- **Glutathione** helps prevent oxidative damage to cells, used to transport AAs across the membranes of cells by the γ-glutamyl cycle.
- **Generation of ribose-5-phosphate for nucleotide biosynthesis**
  - When NADPH is low, oxidative reactions of the pathway can be used to generate ribose-5-phosphate
  - When NADPH is high, the reversible non oxidative portion of the pathway can be used to generate ribose-5-phosphate from fructose-6-phosphate and glyceraldehyde-3-phosphate.
Pathophysiological mechanisms

A defect of TALDO in the pentose phosphate pathway not only has an effect on organogenesis but also on the function of organ systems after birth. Transaldolase is an important enzyme in the PPP, and its deficiency has been shown to deplete NADPH, glutathione (GSH), and diminish nitric oxide (NO) production, lead to decreased mitochondrial transmembrane potential and mitochondrial mass and reduced adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio in the liver of TALDO−/− mice (Hanczko et al. 2009). In fibroblast and lymphoblast cell lines from a TALDO-D patient, the nucleotides NADPH and NAD+ were also depleted, while ADP-ribose had accumulated. A diminished mitochondrial transmembrane potential was also present, but there was an increased mitochondrial mass, which was associated with increased NO, ATP, and Ca2+. Also, enhanced apoptosis was detected (Qian et al. 2008). The differences found might be related to difference in organ systems or between species. Failure to recycle ribose-5P through the nonoxidative branch, and conversion of C5 sugar phosphates to C5 sugars to C5 polyols converting NADPH to NADH results in decreased NADPH necessary for reductive biosynthesis (such as lipid synthesis, cholesterol synthesis, and fatty acid chain elongation) and leads to secondary depletion of GSH and increased
Transaldolase deficiency (TALDO-D, Eyaid syndrome, OMIM 606003)

- Rare AR IE of PPP first described in 2001 (Verhoeven et al. 2001).
- Presentation: prenatally, with intrauterine growth restriction (IUGR) and/or oligohydramnios
- Neonatal period, with dysmorphic facial features, cardiovascular defects, and hepatosplenomegaly
- Later in life, with a milder phenotype or even no symptoms (one patient described so far).
- Ethnic Background: Middle Eastern, Asian, western Asian/southeast European (Turkey), European, West African
- 81% of parents were consanguineous
Characterization of Transaldo Phenotype

- **Skin** Cutis laxa/wrinkled skin was seen in more thin pigmented skin was seen on distal metacarpal joints (knuckles).
- **Cardiac abnormalities**: Congenital heart defects, such as ventricular septal defect (VSD) and/or atrium septal defect (ASD), Bicuspid aortic valve aortic coarctation, and dextrocardia, CM
- **Hepatic abnormalities**: Hepatomegaly, splenomegaly. Hepatic dysfunction associated with fibrosis and cirrhosis. Decreased hepatic synthetic function (decreased serum albumin and abnormal clotting factors). Two patients received liver transplants for progressive liver dysfunction or development of hepatocellular carcinoma.
- **Hematological features**: Anemia, thrombocytopenia
- **Renal manifestations** Proximal and distal tubular dysfunction (aminoaciduria, proteinuria, and loss of electrolytes) was the most prominent renal feature in TALDO-D, other anomalies noted, and renal stones reported
- **Development and neurological symptoms** was normal in most patients. Some experienced (mild) motor delay. Normal visual and auditory development was noted in 29 patients, with no information in three. Abnormalities were seen in two patients [horizontal nystagmus and sensorineural deafness
- **Gonadal function** In 11/34 patients (32%), abnormal external genitalia were present at birth (3 males with small phallus, 3 females with clitoromegaly, 6 males with cryptorchidism). In six patients, hypergonadotrophic hypogonadism was reported.
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Early onset % ($n = 22$)</th>
<th>Late onset % ($n = 12$)</th>
<th>Total % ($n = 34$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia $^a$</td>
<td>77</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Thrombocytopenia $^a$</td>
<td>77</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>Hepatomegaly $^a$</td>
<td>77</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>Splenomegaly $^a$</td>
<td>45</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>5</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Impaired coagulation $^a$</td>
<td>41</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac abnormalities $^a$</td>
<td>68</td>
<td>50</td>
<td>62</td>
</tr>
<tr>
<td>Abnormal skin $^a$</td>
<td>68</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Cutis laxa/wrinkled skin $^a$</td>
<td>59</td>
<td>42</td>
<td>53</td>
</tr>
<tr>
<td>Triangular facies $^a$</td>
<td>41</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Tubulopathy</td>
<td>32</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Renal stones</td>
<td>14</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Hypergonadotropic hypogonadism</td>
<td>27</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Abnormal genitalia $^a$</td>
<td>36</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>Decreased growth-height</td>
<td>36</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>IUGR $^a$</td>
<td>32</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Mild intellectual disability or motor delay $^b$</td>
<td>43 ($n = 14$)</td>
<td>9 ($n = 11$)</td>
<td>28 ($n = 25$)</td>
</tr>
<tr>
<td>Hearing/vision abnormal</td>
<td>5</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Hypotonia $^a$</td>
<td>27</td>
<td>8</td>
<td>21</td>
</tr>
</tbody>
</table>

$IUGR$ intrauterine growth restriction  

$^a$ Feature of presentation  

$^b$ Not able to determine in the younger children
Treatment is supportive
NAC provided
Liver transplant done in 2
Outcomes not mentioned
The biochemistry, metabolism and inherited defects of the pentose phosphate pathway: A review
WE MADE IT !!!!!
IT'S FRIDAY !!!!

Any Questions?
Thank you for attending!
Please leave feedback for this session using the QR code below or use this link.

Recordings of lectures (and handouts, if applicable) will be found later today at our dropbox until a permanent place is found.