Chloe Yuan, Joyce Yeo, Mark Graubart

Case Study #5: Kicked While She's Down
BC362: Medical Biochemistry

Case background:
An 8-year-old girl, Lucy, was brought to the emergency room on a hot summer day by her parents after complaining of intense pain in her legs. Her mother tells you that the pain began after Lucy's first-ever soccer practice. In addition to being in pain, Lucy appears shaky and is sweating profusely. During the physical exam, you noted that Lucy is at the 15th percentile for both her height and weight compared to other girls her age. While talking with her mother to gather more details, she tells you that there is no family history of metabolic diseases, but tells you that Lucy has always been extremely lethargic early in the mornings. Additionally, the father reveals that he and Lucy's mother are consanguineous. Given Lucy's symptoms and her medical background, you order genetic testing, which reveals she has a mutation in the PGM1 gene. You diagnose her with phosphoglucomutase-1 (PGM1) deficiency. Lucy's lab results are shown below.

Clinical Findings:
Table 1. Blood testing upon admission

	Upon Admission	Normal Range
Blood Glucose	32.4 mg/dL	70–100 mg/dL
Creatine Kinase	500 IU/L	10-300 IU/L
Myoglobinuria	Present	Not present

Given these results, IV fluids are administered to minimize kidney damage, and IV dextrose is administered. Additionally, you prescribe that Lucy take 1 gram of D-galactose per kilogram of body weight every day.

Biochemistry:

Phosphoglucomutase deficiency, a congenital disorder of glycosylation, impairs the interconversion of glucose-1-phosphate (G1P) and glucose-6-phosphate (G6P). This can result from mutations in the PGM1 gene located on chromosome 1, which encodes the enzyme phosphoglucomutase-1 (PGM1).

Under normal physiological conditions, PGM1 catalyzes the reversible transfer of a phosphate group between the 1 and 6 positions of glucose phosphate. This reaction links glycogenesis, which uses PGM1 to make G1P, and glycogenolysis, which uses PGM1 to make G6P. In hepatocytes and skeletal muscle cells, PGM1 is essential for stored glycogen to be efficiently mobilized into glucose for energy or, conversely, enables glucose to be stored as glycogen.

When PGM1 is deficient, both glycogen breakdown and synthesis become inefficient, leading to impaired glucose homeostasis and defective energy metabolism, particularly during fasting or exercise. In muscle tissue, this defect manifests as exercise intolerance, muscle cramps, and rhabdomyolysis, while in the liver, patients may experience hypoglycemia and abnormal glycogen accumulation.

Vocabulary: Consanguineous, PGM1, rhabdomyolysis, hypoglycemia, hepatocytes

Discussion Questions:

1) What is the primary biochemical explanation for the values found in Table 1?
2) Given Lucy's PGM1 deficiency, how does the administration of IV dextrose improve Lucy's symptoms?
3) Given Figure 1 and what we have covered in class, provide an explanation as to how D-galactose ingestion serves as a long-term treatment for Lucy's hypoglycemia. Will she still have exercise intolerance?

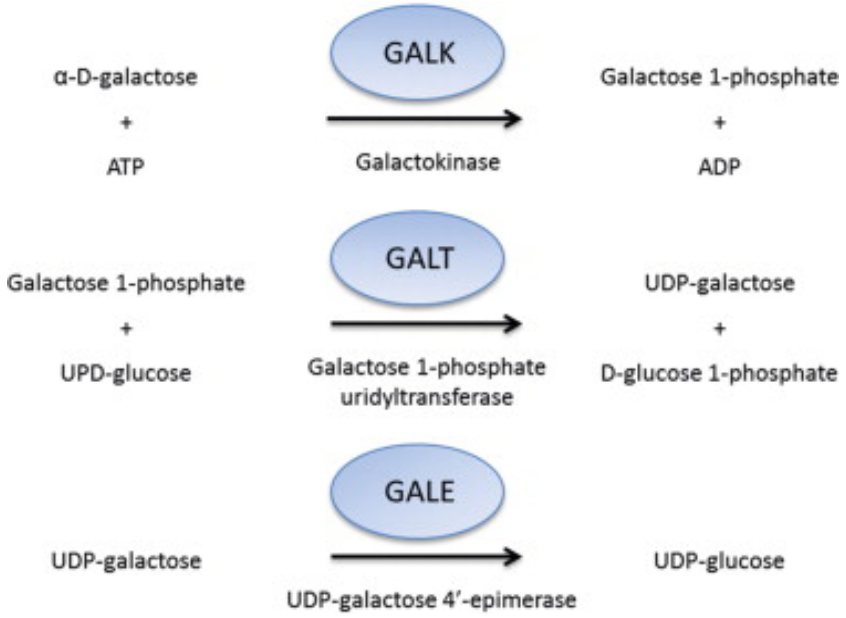

Figure 1: Leloir Pathway

References:

- Conte, F., et al. (2020, October). *Phosphoglucomutase-1 deficiency: Early presentation, metabolic management and detection in neonatal blood spots*. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1096719220301852
- *Leloir Pathway*. (n.d.). ScienceDirect. https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/leloir-pathway
- Quick, C. B., Fisher, R. A., & Harris, H. (1974, March). *A Kinetic Study of the Isozymes Determined by the Three Human Phosphoglucomutase Loci PGM1, PGM2 and PGM3*. Wiley. https://febs.onlinelibrary.wiley.com/doi/full/10.1111/j.1432-1033.1974.tb03366.x
- Tegtmeyer, L. C., et al. (2014). *Multiple Phenotypes in Phosphoglucomutase 1 Deficiency*. The New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa1206605
- Yokoi, K., et al. (2018, May). *Disruption of the responsible gene in a Phosphoglucomutase 1 deficiency patient by homozygous chromosomal inversion*. PMC Home.

Answers

Vocabulary:

- Consanguineous: describing two individuals related by blood
- PGM1: the gene that encodes the production of the phosphoglucomutase-1 protein
- Rhabdomyolysis: a medical condition characterized by the breakdown of muscle tissue
- Hypoglycemia: deficiency of glucose in the bloodstream.
- Hepatocytes: liver cells

Discussion Questions:

1) Given Lucy's PGM1 deficiency, her ability to carry out glycogenesis and glycogenolysis is incredibly hindered. After a session of relatively intense exercise, her low glycogen stores and her inability to break down glycogen result in extreme hypoglycemia. Without the presence of G6P, a product of glycogenolysis, muscle cells are unable to carry out glycolysis at an efficient rate, thereby preventing the production of ATP. Because of this, the strenuous exercise caused an energy deficiency, which resulted in cell lysis, leading to the presentation of rhabdomyolysis, characterized by brown urine, muscular pain, myoglobinuria, and elevated levels of creatine kinase in blood.

2) Lucy is given IV dextrose to increase her blood sugar, which is causing her shakiness and profuse sweating. Because dextrose is chemically identical to glucose, it does not need to be metabolized via glycogenesis or glycogenolysis. With this being the case, administration of IV dextrose will directly increase the amount of free glucose in Lucy's bloodstream regardless of her PGM1 deficiency, increasing her blood sugar and alleviating the shaking and sweating caused by hypoglycemia.

3) As seen in Figure 1, D-galactose metabolism results in the formation of G1P and UDP-galactose. The UDP-galactose is then modified with GALE to produce UDP-glucose, which can then be used to carry on the Leloir pathway or enter glycogenesis. The G1P can also be used for glycogenesis, thereby increasing Lucy's glycogen stores. Thus, dietary D-galactose provides an alternative source of G1P and UDP-glucose when PGM1 is not functioning. In the liver, there are the isozymes PGM2 and PGM3, which are still partially active in patients with PGM1. The residual PGM activity allows the partial conversion of G1P to G6P, leading to limited glucose production after dephosphorylation by G6Pase.

   Unfortunately, Lucy will still experience some degree of exercise intolerance, as she lacks a sufficient means of producing enough G6P, especially in a quick manner. Given this, her muscles will be unable to carry out glycolysis for an extended period.