Ava Oseback, Naji Yerokun, Rachel Park

Case Study #6: Lactic Attack: *A Metabolic Meltdown*
BC 362, Medical Biochemistry

Case Background:

A 7-month old female named Tabitha is rushed into the emergency room by her parents. Tabitha's consanguineous parents report numerous attacks of hyperventilation following a first attempt at feeding with Gerber Baby "Apple Pear" food pouches in hopes of steadily weaning her off breastmilk following feeding for 6 months. Tabitha presents with severe lactic acidosis (20 mM) and hypoglycemia. After administering sodium bicarbonate, your resident, Dr. Millard, asks you to place Tabitha on a high-carbohydrate diet and to perform a physical examination. Your physical examination was consistent with hepatomegaly. You perform a glucagon tolerance test. Glucagon produced a glycemic response after 6 hr, but not after 18 hr of fasting. 18 hours after stabilization on the high carbohydrate diet, Tabitha presents with hypoglycemia (plasma glucose 40 mg/100 ml), lactic acidosis (6-10 mM), and a rise in plasma alanine. Intravenous galactose increased plasma glucose but intravenous fructose, glycerol, and alanine caused a 40-50% fall in plasma glucose and a significant rise in lactate (Δ 3-4 mM).

Following a sudden code blue and a page, Dr. Millard dashes away and asks you and your fellow interns to take care of Tabitha. You decide to order a series of panels. Results are as follows:

Laboratory Results:

Table 1. Initial test results.

	Upon Admission	Normal
RBC panel	4.7/mm³	3.90–5.50/mm³
Hematocrit	36%	34-40%
Lactate	20 mM/L	1-3.3 mM
Blood Glucose	1.7 mM/L	3.5mM/L - 5.56 mM/L
pH	6.92	7.35 - 7.45
CO_2	16 mmHg	21 - 41 mmHg
GSH:GSSG	270:1	> 200:1

Table 2. Concentrations of hepatic intermediates.

	Patient (umols/kg)	Normal (umols/kg)
Glucose-6-phosphate	119.5	273.0 ± 29.5
Fructose-6-phosphate	11.4	27.0 ± 1.8
Fructose-1,6 -biphosphate	43.7	25.0 ± 2.2
Pyruvate	14.5	106.0 ± 6.9
Lactate	2980.0	1820.0 ± 160.0

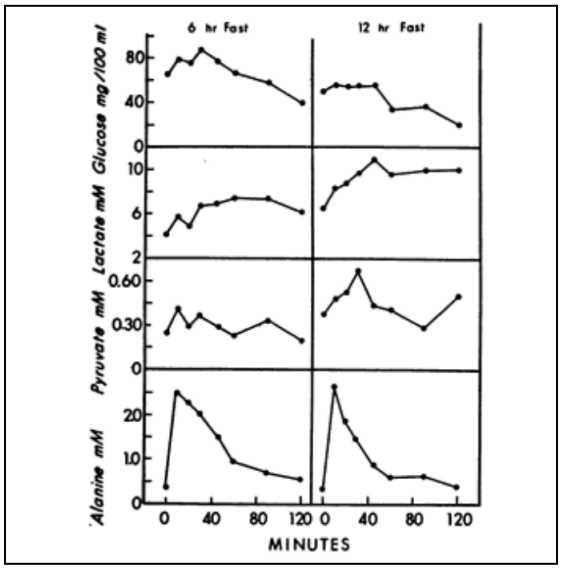

Figure 1. Glucagon tolerance test. Intramuscular glucagon, .5mg, was given after 6- and 18-hr fasts

Differential Diagnoses:

1. Impaired Glycogenolysis: *Glycogen phosphorylase deficiency*
2. Impaired PPP: *G6PDH Defect*
3. Galactosemia
4. Impaired Gluconeogenesis: FBPase Deficiency

Discussion Question:

1. How do the background and lab results allow us to rule out the potential diagnoses?

Biochemistry:

Fructose 1,6-bisphosphatase (FBPase) deficiency is a disorder of gluconeogenesis by mutation in the FBP1 gene on chromosome 9. The deficiency blocks the irreversible conversion of fructose 1,6-bisphosphate (F1,6BP) to fructose 6-phosphate (F6P), an important step in glucose homeostasis. Under normal physiological conditions, FBPase catalyzes the rate limiting step in gluconeogenesis, removing a phosphate group from F1,6BP.

When FBPase is deficient, there is a build up of F1,6BP, which causes an upstream accumulation of lactate, pyruvate and amino acids. This defect manifests as hypoglycemia, lactic acidosis and hyperalaninemia.

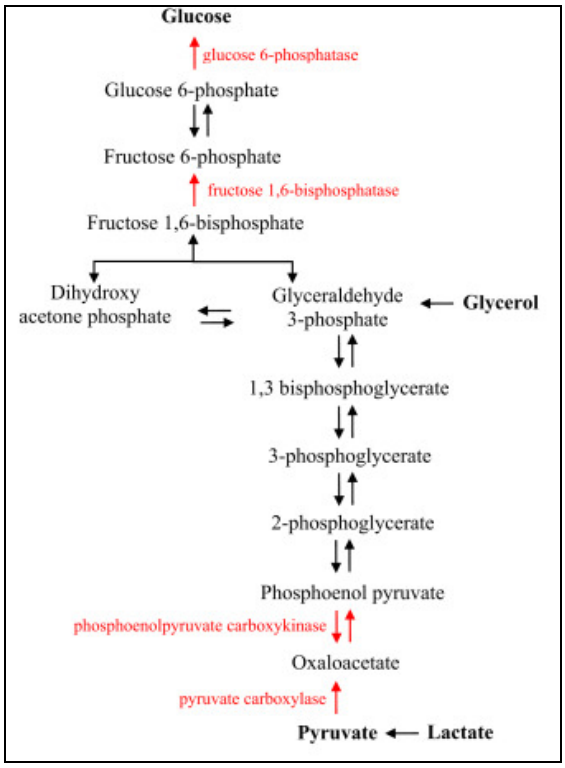

Figure 2. Gluconeogenesis pathway diagram

Important Vocabulary:

Hepatomegaly - *Enlarged liver*

Hyperalaninemia - *Abnormally high levels of alanine in the blood*

GSH:GSSG - *Reduced glutathione (GSH) to oxidized glutathione (GSSG) ratio*

Further Discussion Questions:

2. What types of foods should the parents avoid giving her? What can be given to prevent hypoglycemia?
3. A fellow intern suggests that you administer a fructose tolerance test to confirm your conclusion. You have reservations about this. What should you probably do and why?

Important Information:

Fructose 1,6-bisphosphatase deficiency is a rare autosomal recessive disorder and only approximately 150 people have been affected (2019). They mainly affect infants and young children, where symptoms are usually present shortly after birth.

References:

Bijarnia-Mahay, Sunita. *Fructose-1,6-Bisphosphatase Deficiency.* GeneReviews [Internet]., U.S. National Library of Medicine, 5 Dec. 2019, www.ncbi.nlm.nih.gov/books/NBK550349/.

Pagliara, Anthony, et al. "Hepatic fructose-1,6-diphosphatase deficiency: A cause of lactic acidosis and hypoglycemia in infancy." *The Journal of Clinical Investigation*, vol. 51, 1972, pp. 2115-2123.

HOWELL, R R et al. "Glucose-6-phosphatase deficiency glycogen storage disease. Studies on the interrelationships of carbohydrate, lipid, and purine abnormalities." Pediatrics vol. 29 (1962): 553-65.

Answers:

Discussion Questions:

1.
    a. **Impaired Glycogenolysis: Glycogen phosphorylase deficiency |** After administering a glucagon tolerance test, you confirmed that Tabitha exhibited a glycemic response. This response suggests that glycogen phosphorylase's glucosidase activity is preserved. That being said, in infants this glycemic response (dependent on availability of glycogen) subsides between 2 ~ 12 hours. In order to replenish glycogen stores, a healthy infant's liver would buffer blood glucose levels via activation of gluconeogenesis. The background as well as **Figure 1** demonstrate that *after* the 6 hour fast, these glycogen stores are not adequately replenished and blood glucose drops significantly, suggesting impairment in a system other than glycogenolysis.

    b. **Impaired PPP: G6PDH Defect |** The results of the RBC panel and hematocrit test argue that Tabitha's biochemical systems are adequately preventing buildup of oxidative stress that would regularly result in damaged RBC membranes and impaired circulation. More conclusively, the GSH:GSSG ratio also appears normal. A hallmark of a functioning Pentose Phosphate Pathway (PPP) is the production of NADPH and subsequent use of this coenzyme to facilitate reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH). GSH is used to "detoxify" reactive oxygen species like H2O2 and superoxide. Instead, it is a ***low ratio*** of GSH:GSSG **(<< 200:1)** that would suggest an impairment of the PPP.

    c. **Galactosemia |** This one is subtle! Information from the background section suggests that Tabitha was completely fine while maintained on her breastmilk diet. Breastmilk is rich lactose. The monosaccharides that make up this disaccharide are glucose and galactose. Galactose *enters* the glycolysis/gluconeogenesis pathway as Glucose-6-Phosphate, meaning that it does not need to first be converted from F1,6BP to F1P.

2. As Tabitha is experiencing symptoms resulting from overconsumption of fructose and a defect with FBPase, we can presume that offering her a diet high in fruit might not be the greatest idea. Instead, it may be a good idea to supplement her diet with complex carbohydrates like starch which can slowly be broken down into glucose, or a diet high in lactose, which will be broken down into glucose and galactose. This would replenish Tabitha's glycogen stores, combatting hypoglycemia, while providing fuel for continued glycolysis!
3. A fructose tolerance test would be dangerous and unnecessary! Laboratory results confirm a buildup in fructose-1,6-biphosphate and an analogous decrease in the hepatic concentration of fructose-6-phosphate and glucose-6-phosphate. This suggests that there is certainly an impairment in fructose metabolism. This impairment has resulted in Tabitha's increased Lactate levels, incurring subsequent lactic acidosis and hyperventillation. Supplying 7-month-old Tabitha with high amounts of fructose may have more undesirable effects than she can tolerate. Instead, you might consider enzyme activity assays, sequencing, and other ways of confirming an abnormality in Tabitha's Fructose-2,6-Phosphatase activity.