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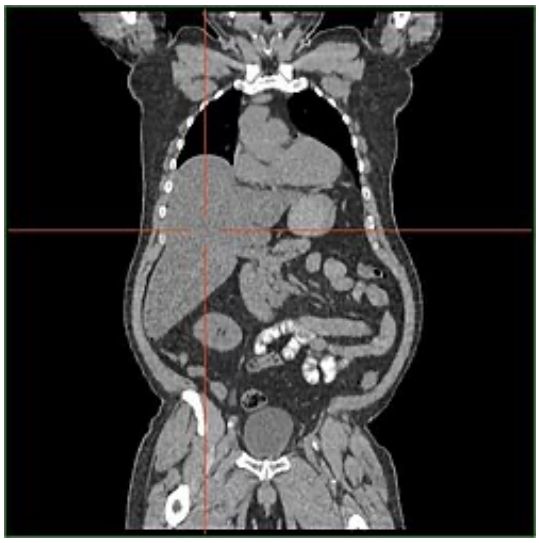
Student Case Study #3: Starved in the Midst of Plenty
BC362: Medical Biochemistry

Case Background:
A four-month-old infant named Charlie is brought into the pediatric emergency room by his parents. They are concerned because he repeatedly becomes irritable and shaky several hours after eating. Upon physical examination, you note that Charlie's abdomen feels swollen, and his growth is below the 10th percentile for his age. During the visit, you notice him becoming lethargic and diaphoretic (sweating excessively). After performing a fasted glucose test, you admit Charlie for further evaluation. His genetic testing results show a mutation in the *G6PC* gene and the doctors diagnose him with Glycogen Storage Disease Type 1a (GSD1a), also known as Von Gierke disease. Charlie's initial laboratory results and imaging are provided below.

Clinical Findings:
Table 1. Initial laboratory results upon admission.

	Upon Admission	**Normal Range**
Blood Glucose (fasted)	28 mg/dL	70–100 mg/dL
Lactate	7 mmol/L	0.5–2.2 mmol/L
Blood pH	7.30	7.35–7.45
Total cholesterol	213 mg/dL	100-150 mg/dL

Figure 1. Imaging reveals enlarged liver (hepatomegaly) shown in the crosshairs.



Biochemistry:
Glycogen Storage Disease Type 1a (GSD1a), or Von Gierke disease, is an autosomal recessive disorder in which there is a mutation on the *G6PC* gene on chromosome 17 that encodes for glucose-6-phosphatase (G6Pase). Typically, G6Pase removes a phosphate group from glucose 6-phosphate, and the resulting glucose molecule is secreted into the bloodstream via GLUT2 transporters. (Refer to slide 7 from last Friday's lecture for a reminder of this pathway.)

The mutated G6Pase is unable to catalyze this reaction and prevents the final step of glycogenolysis and gluconeogenesis from occuring. Ultimately, this enzyme deficiency leads to an ineffective conversion of glucose-6-phosphate to glucose in the liver.

This deficiency also causes compensatory metabolic pathways to be activated, ultimately resulting in hyperlipidemia, hypercholesterolemia, hyperuricemia, and lactic acidosis, as observed in the laboratory results.

Vocabulary: Hepatomegaly, diaphoretic, hyperlipidemia, glycogenolysis, gluconeogenesis

Discussion Questions:

1. Provide a biochemical explanation for Charlie's hepatomegaly.
2. Charlie's muscles are less affected by the disease than one might expect, with only some mild muscle weaknesses noted at this time. Explain this observation, given the different fates of glucose 6-phosphate in the muscle and the liver.
3. What interventions would you recommend for this patient to help overcome the dysregulation in glucose homeostasis?

References

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Answer Key

Vocabulary:

- **Hepatomegaly**: enlargement of liver
- **Diaphoretic**: appears excessively sweaty
- **Hyperlipidemia**: high levels of lipids in the bloodstream, including cholesterol and triglycerides
- **Glycogenolysis**: the breakdown of glycogen into glucose
- **Gluconeogenesis**: the process of creating glucose when blood glucose levels are low (reverse of glycolysis)

Discussion Questions:

1. Provide a biochemical explanation for Charlie's hepatomegaly.
    a. Because the mutated G6Pase is unable to effectively convert G6P to glucose, the amount of glycogen in the liver accumulates. This means the liver begins to store excess glycogen, which contributes to the development of fatty liver and causes an overall increase in the size of the liver.
2. Charlie's muscles are less affected by the disease than one might expect, with only some mild muscle weaknesses noted at this time. Explain this observation, given the different fates of glucose 6-phosphate in the muscle and the liver.
    a. In the muscles, glucose 6-phosphate enters glycolysis directly, where it is converted into pyruvate to provide ATP for muscle contractions. The muscles do not need to convert glucose 6-phosphate to glucose to secrete via GLUT2 transporters like the liver does. As such, G6Pase is not as essential for muscle function.
3. What interventions would you recommend for this patient to help overcome the dysregulation in glucose homeostasis?
    a. The best course of treatment to regulate Charlie's hypoglycemia would be to modify his diet to include several small meals throughout the day that are high in carbohydrates and low in fructose, galactose, and sucrose. To maintain Charlie's blood glucose levels overnight, uncooked cornstarch should be used before bed because it allows for the steady release of carbohydrates during long periods of fasting (1.6 g/kg of cornstarch every 3 to 4 hours for young children). To manage Charlie's hyperlipidemia, a diet that is low in fat and high in protein should be maintained. Recurring hypoglycemia could lead to cerebral damage or cognitive impairment, so adhering to a firm diet plan is crucial.
    b. Early diagnosis, managing metabolism, strict diet, and frequent liver function tests allow for patients to lead normal lives. Liver transplant may be considered if liver complications become severe.