The Case of Bhufus Bealer

The head of the geriatrics unit informed me of a peculiar case of an elderly patient, Bhufus Bealer, a 62-year-old male from Bald Knob, Arkansas. Mr. Bealer came to the Central Arkansas Geriatrics Clinic complaining of misdiagnosis of von Gierke disease. According to Mr. Bealer, his doctor diagnosed him with the condition in 2003, when Mr. Bealer was 59 years old. After contacting his doctor, I learned that he was diagnosed based on the following symptoms: 1) the patient's blood glucose levels did not significantly rise, even after a carbohydrate-rich meal; 2) the patient was underweight due to low concentrations of lipid, suggesting that the patient relies heavily on fat metabolism; 3) the patient was ketotic; 4) the patient had labored breathing. Surprisingly, however, the patient's liver size was not assessed. The treatment was putting the patient on a high carbohydrate diet.

Mr. Bealer complained that the treatment was not having any effect on the relief of his symptoms; rather, his symptoms only worsened. We conducted further physical examinations, and found that the patient was indeed underweight and had labored breathing. We also found that the patient exhibited signs of fatigue even after small activities, frequently urinated, was dehydrated, had low blood pH, and was ketotic. Mr. Bealer also complained of being constantly hungry.

Several subsequent tests suggested that Mr. Bealer was indeed misdiagnosed. An MRI revealed that Mr. Bealer's liver was of normal size, not swollen as would be expected in von Gierke disease. Furthermore, upon administration of glucagon and epinephrine, the patient's blood glucose levels did rise, which would not happen if glycogen degradation was inhibited as in von Gierke disease. However, the blood glucose levels dropped off unusually rapidly after that. I suspected that Mr. Bealer had an enzyme deficiency in either glycolysis or the Kreb's cycle, but further tests were needed to confirm my suspicions. I ordered the following lab work to be done on the patient.

Solutes	**Patient Levels**	Normal Levels
Blood Glucose	35 mEq/L	70-110 mEq/L
Blood Urea Nitrogen	80 mEq/L	5-25 mEq/L
Deoxy Hb	0.8 mg/dL	0.5 mg/dL
Oxy Hb	0.4 mg/dL	5 mg/dL
Insulin	Elevated	Normal
White Blood Cell Count	Normal	Normal
pCO_2	90 mm Hg	35-45 mm Hg
Blood pH	6.9	7.2
Glutamate	350.0 mmol/mol creatinine	20.0 – 200.0 mmol/mol creatinine
Lactate	20.0 mmol/mol creatinine	0.0 – 100.0 mmol/mol creatinine
NH_4^+	200 mEq/L	20 mEq/L
Coenzyme A	10.0 mg/dL	0.2 – 1.0 mg/dL
Glucagon	Elevated	Normal
Carnitine	150 mEq/L	20 mEq/L

An organic acid test produced the following data.

Compound	**Patient Value mmol/mol of creatinine**	Reference Range mmol/mol of creatinine
Oxaloacetate	60.0	30.0 – 40.0
Citrate	430.0	180.0 – 560.0
Pyruvate	70.0	0.0 – 50.0
α-ketoglutarate	475.0	15.0 – 200.0
Succinate	2.0	0.0 – 20.0
Fumarate	1.5	0.0 – 10.0
2-hydroxybutyrate (ketone bodies)	0.0 – 2.0	8.0

I found that treatment with vasopressin greatly improved the patient's condition. Vasopressin is a drug that has been clinically shown to increase the metabolic rates of the α–ketoglutarate dehydrogenase complex. From the organic acid test results, it is clear that α–ketoglutarate levels are much higher than a subsequent product, succinate; therefore, I conclude that Mr. Bealer suffers from a deficiency in α-ketoglutarate dehydrogenase. It is no wonder that Mr. Bealer complained of the high-carb diet his doctor prescribed; such a diet only increases the activity of the pathways, leading to even higher levels of α–ketoglutarate.

I knew that a deficiency in this enzyme was also linked to several neurodegenerative disorders, including Alzheimer's and Parkinson's diseases. I

conducted several memory tests on Mr. Bealer to determine the presence or extent of the diseases. Sadly, Mr. Bealer was found to be in the early stages of Alzheimer's diseases.

I entered the following pages into my personal journal.

Dear Journal,

I had the most unusual case this afternoon. It appears that a Mr. Bhufus Bealer, a resident of Bald Knob, has become deficient in a very important metabolic enzyme: α-ketoglutarate dehydrogenase. Let me explain how I arrived at this conclusion.

First of all, I had Mr. Bealer describe his symptoms to me. They included labored breathing, increased appetite, lethargy, and fatigue after the slightest muscle activity. I gave him a complete physical and found further that he had very low fat counts, low blood glucose levels, poor muscle tone, slight ketosis, and low blood pH. His doctor erroneously diagnosed him with von Gierke disease, which is understandable since the symptoms do seem to suggest that. However, I was able to rule out that disease by the methods described in the case study.

Let me explain how a deficiency in the α-ketoglutarate dehydrogenase complex could illicit such symptoms.

Labored Breathing. The complex is an important control point within the TCA cycle, which is responsible for the regeneration of reducing cofactors such as NADH and $FADH_2$. If the complex is present in only small amounts, it will take more time for these cofactors to be produced. These cofactors are then shipped off to the oxidative phosphorylation process to produce much-needed ATP. However, if the cofactors are being generated only slowly, then the ATP produced will not be enough to satisfy the body's basic need for energy. Thus, the body, seeing the energy deficiency as a problem with oxidative phosphorylation, begins to demand more oxygen to try to solve the problem. How does one take in oxygen? By breathing, of course! And the only way to get more oxygen is to breathe more; hence Mr. Bealer's rapid breathing.

Increased Appetite. Because of the deficiency in ATP, the glycolytic pathway is not inhibited. This means that any glucose present will be taken to pyruvate, then to acetyl-CoA, then thrown into the TCA cycle. However, ATP production is still not increased, so the body demands more glucose. This increases insulin in the blood which triggers the desire for food, explaining Mr. Bealer's appetite problem.

Lethargy and Fatigue. I have already addressed the decrease of ATP production. With limited ATP, the body has to prioritize what organ gets to be served first. Thus, Mr. Bealer becomes tired out very easily because the body cannot allocate a constant supply of ATP to his muscle cells.

Low Fat Count. With so little ATP available, the body does everything it can to try to alleviate the problem. This means that any lipids present are going to undergo β-oxidation to form acetyl-CoA and G-3-P. The body is so desperate for energy, it utilizes all available lipids in this way.

Low Blood Glucose Levels. Similarly, any glucose in the blood is shipped almost immediately into the cells to undergo glycolysis.

Poor Muscle Tone. The high levels of glucagon and epinephrine turn on glycogen degradation in both the liver and the muscles. The glycogen is degraded but glycogen synthesis is never activated. Thus, the muscles lose significant mass. Also, if given enough time without food, the muscles will begin to metabolize any available amino acids, further decreasing muscle mass.

Slight Ketosis. Because the body is deficient in energy, glucose and lipids are being converted into acetyl-CoA. This leads to high concentrations of acetyl-CoA, and the body gets rid of this by synthesizing ketone bodies. In essence, the body believes it is starving.

Low Blood pH. The buildup of a-KG causes a problem. It can't be metabolized fast enough into amino acids or into succinyl-CoA. Therefore, the elevated levels of the organic acid begin to donate protons to the bicarb buffer system, thus lowering the pH.

I'd like to now take a look at how this enzyme deficiency affects different metabolic pathways in the body.

Glycolysis. Glycolysis takes place as soon as glucose hits the bloodstream and can be absorbed by the cell. Glycolysis runs uninhibited because none of its three control points – phosphofructokinase, hexokinase, and pyruvate kinase – are being inhibited. Glucose is being taken to pyruvate, and pyruvate is being taken to acetyl CoA. There is not enough ATP present in the cell to inhibit pyruvate kinase, so glycolysis will run as long as there is glucose present. The high level of glycolytic activity and the cell's need for glucose caused Mr. Bealer's low blood-glucose levels.

Gluconeogenesis. When Mr. Bealer's glucose stores are depleted, the liver will begin to run gluconeogenesis to generate more glucose. This pathway is costly, but the cell thinks it can generate more ATP by producing more glucose. Thus, the problem becomes even more compounded. Gluconeogenesis utilizes Mr. Bealer's stores of fatty acids to produce pyruvate and take it to glucose.

Glycogen Metabolism. The low blood-sugar levels trigger the release of glucagon by the pancreas. This initiates glycogen degradation in the liver into glucose-6-phosphate, which can then enter glycolysis or the pentose-phosphate pathway. Glycogen degradation is also stimulated in the muscle cells by epinephrine to provide more glycolytic intermediates. This is why Mr. Bealer complained of muscle fatigue after little muscular activity; his glycogen stores are constantly depleted due to the body's energy deficiency.

Pentose-phosphate pathway. Undoubtedly, much of the glucose-6-phosphate generated by gluconeogenesis enters into the pentose-phosphate pathway because NADPH and ATP can be produced. This causes a rise in CO_2 and H^+ levels, but the cell has to prioritize according to its need. The elevated levels of these two compounds contributes to the already lowered blood pH.

Citric Acid Cycle and Oxidative Phosphorylation. This is where the enzyme deficiency has its largest effect. As one of the control points of the citric acid cycle, a-ketoglutarate dehydrogenase plays an important job in the cycle. It is inhibited by succinyl-CoA, ATP and NADH; in which the cell is very deficient.

Thus, although deficient in the enzyme, the citric acid cycle will continue to run; and, since α-ketoglutarate cannot be reacted very quickly, there will be a monstrous buildup of this compound unless something is done to dissipate that buildup. Through the enzyme glutamate dehydrogenase, some of the excess α-ketoglutarate can be formed into glutamate, of which we would expect to see high levels. The presence of so much α-ketoglutarate, an organic acid, also helps to lower the blood pH. The glutamate, however, can be metabolized into urea, as I will address later on.

Thus, with the citric acid cycle seriously impeded, and at such an early stage, very little coenzymes will make it to the oxidative phosphorylative stage. This causes a severe energy crisis, and the cell, thinking it is starving to death, quickly utilizes all possible pathways to generate more energy.

Fatty Acid Metabolism. Fatty acids are degraded as quickly as possible through lipolysis. From the adipocyte, a fatty acid can be oxidized to form glycerol, which can be taken all the way to G-3-P and into glycolysis or gluconeogenesis; or, a fatty acid can be oxidized to form acetyl CoA. Due to the increased activity of lipolysis, I expected to find high amounts of carnitine and coenzyme A, which I did. The oxidation of these fatty acids also produces much needed cofactors, such as NADH and $FADH_2$.

Protein Metabolism. The excess α-ketoglutarate is aminated to form glutamate via glutamate dehydrogenase. The glutamate then becomes concentrated, and the cell must look for a way to dissipate that concentration. The glutamate is oxidatively deaminated to yield ammonium ion. The ammonium ion can then be combined with the amino group from aspartate to form urea. This urea is then excreted from the body as urine. The excess of urea in the body explains Mr. Bealer's high amount of blood urea nitrogen. If Mr. Bealer goes for a lengthy period of time without eating, the muscles will begin to actually metabolize their own proteins into glycolytic and gluconeogenic intermediates.

I have to admit that it was one of the most interesting cases I ever had to deal with. Today, Mr. Bealer enjoys a normal life due to the medication that has been prescribed him. The Alzheimer's disease was caught early enough that little damage was done to the brain, and his doctor predicts a long, healthy life ahead.

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1. Blood Glucose: blood glucose is lowered because the body is utilizing every scrap of glucose to generate energy, running it through glycolysis in the cytoplasm.
2. Blood Urea Nitrogen: levels are elevated due to excess urea in the body. The urea is a result of excess of α–ketoglutarate, which is aminated to form glutamate, which is deaminated to form ammonium ion, which combines with another amino group to form urea.
3. Deoxy Hb: levels are slightly high because blood pH is low and favorable to the T form. The levels are also high because CO_2 concentration is elevated.
4. Oxy Hb: levels are slightly low because deoxy levels are high
5. Insulin: levels are elevated because energy levels are low – glucose in the blood must be transferred to the cytoplasm of a cell to undergo glycolysis.
6. WBC count: normal because the patient is not suffering from an infection
7. pCO_2: a little high because the formation of NADPH and ATP via the pentose-phosphate pathway generates 3 molecules of CO_2.
8. Blood pH: low because buildup of α–ketoglutarate donates protons to the bicarb buffer system.
9. Glutamate: high because excess α–ketoglutarate is being formed into this to get rid of it.
10. Lactate: low levels because it is being converted to glucose via gluconeogenesis as fast as it is formed
11. NH_4^+: high because urea cycle is very active in ridding the body of excess α–ketoglutarate
12. Coenzyme A: high because oxidation of fatty acids is high to produce energy rich compounds
13. Glucagon: elevated because blood-glucose levels are low
14. Carnitine: high because it is necessary for β-oxidation of fatty acids, which is highly active in the body.
15. Oxaloacetate: high because both the TCA cycle and gluconeogenesis are being run, and OAA is part of both.
16. Citrate: normal because TCA cycle is not inhibited before this step, and citrate is able to be converted to isocitrate.
17. Pyruvate: high because gluconeogenesis, TCA cycle, and glycolysis are being run, and it is present in all three pathways.
18. α–ketoglutarate: high because α–ketoglutarate dehydrogenase, which catalyzes the next step, is inhibited. This causes a massive buildup of α–ketoglutarate.
19. Succinate: low because the TCA cycle is inhibited before this step; therefore, very little α–ketoglutarate can be converted to succinyl-CoA, and very little succinyl-CoA can be converted to succinate.
20. Fumarate: low for the same reasons as succinate.
21. 2-hydroxybutyrate (ketone body): high because glucose levels are low, acetyl-CoA levels are high and have to be dissipated.