CLINICAL VIGNETTE

Ketoacidosis in a Non-Diabetic Patient

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A 34-year-old woman, presented to the hospital with shortness of breath and chest tightness along with weight loss of twenty pounds over the prior two months. She also complained of dizziness and palpitations. She had previously been in good health and had an uncomplicated delivery of a healthy son about one year prior. She continued to breastfeed and reported that he would request feeding every one to two hours daily including many nights. She felt her weight loss was due to being unable to eat enough food to keep up her milk production. She had no previous past medical history, family or personal history of diabetes mellitus. She did not take any prescribed or over the counter medications.

She denied fever, chills or diarrhea. She had no sick contacts and all members of her household were well. She denied alcohol or illicit substance use and she stated that her mood was euthymic. When she presented to the emergency department, she was afebrile but was tachycardic at 104 beats per minute. She had slight tachypnea with a respiratory rate of twenty-two breaths per minute. Her body mass index was 18.7. Physical exam had no significant findings on her head and neck exam. She had clear breath sounds and normal heart sounds although she was tachycardic. Her abdomen was soft and non-tender without palpable organomegaly. Her extremities and neurologic exam were unremarkable and her affect and mood were within normal range. Her body mass index (BMI) was 18.7. Her hemoglobin and hematocrit were normal with a white blood cell count of 7.2 $x10^9$/L and platelets of 218/uL. Her metabolic panel was significant for a sodium of 143 mEq/L potassium of 3.2 mEq/L a chloride of 104 mEq/L a bicarbonate of 16 mEq/L and a serum glucose of 105 mg/dL. Her blood urea nitrogen was 7 mg/dL and her creatinine 0.54 mg/dL. Her anion gap was elevated at 23 mmol/L. Her arterial blood gas (ABG) showed a pH of 7.51, and a PCO2 of 21.5 mmHg, a PO2 115 mmHg and bicarbonate 16.8 mEq/L. Her osmolal gap was normal. Analysis of her urine was significant for three plus ketones and no glucose. Her serum beta-hydroxybutyrate level was 1.9 (Range 0.4-0.5 mmol/L). Her chest x-ray (CXR) was normal and her electrocardiogram (ECG) showed diffuse ST depressions. Acetaminophin and Salicylate levels were negative.

Patient was admitted to the hospital and given three liters of intravenous 0.9% saline overnight. By the following day her anion gap had resolved and her serum bicarbonate increased to 22 mEq/L. Her intravenous fluids were changed to 5% dextrose. Given that the patient had no evidence of diabetes and did not have any history of alcohol consumption she was diagnosed with lactation ketoacidosis. She was given strategies to prevent future episodes including the introduction of solids to her infant's diet along with the need to increase her daily caloric intake.

Discussion

An elevated anion gap metabolic acidosis is a frequent finding in hospitalized patients and ketoacidosis is a common cause. This is usually due to uncontrolled diabetes mellitus type one or two. Chronic alcohol abuse and salicylate poisoning also cause the accumulation of multiple acids including ketoacids and should be excluded. Excessive fasting can causes the production of ketone bodies although the degree of acidosis usually remains mild. The normal measured osmolal gap and her medical history helped rule out toxins. A measured plasma osmolality was done to estimate the osmolal gap. Generally, an unexplained, large osmolal gap is strong evidence of methanol, ethylene glycol, or isopropyl alcohol use. A history of recent ethanol intake must be excluded. The osmolal gap is the difference between the measured osmolality and the calculated plasma osmolality.

Lactation ketoacidosis was originally discovered in cattle where it is known as bovine ketosis.[1] The pathophysiology involves the net energy loss from more calories being lost in the formation of breast milk than are ingested. This pathophysiologic process results in the same ketoacid production as in diabetic ketoacidosis. In our patient, her quick recovery was likely due to intravenous fluid induced ketone and acid excretion by her kidneys, carbohydrate (dextrose) infusion post saline with subsequent insulin stimulation and secretion suppressing further lipolysis and ketone body formation.[2]

The nutrient intake of a lactating mother requires at least five-hundred kilocalories per day (kcal/day) in the first six months and four hundred kcal/day up to the end of the first year postpartum.[3] If this level of food intake is not met there is a strong likelihood of developing a negative caloric balance. This may be exacerbated by dieting, concomitant infections or other stressors. Increasing caloric demand that is required for lactation further depletes glucose and other complex carbohydrate stores. This ultimately eliminates liver glycogen reserves and generates ketone body formation. This in turn manifests as a metabolic acidosis from ketonemia.[4]

A word on terminology, we use the term "ketoacidosis" in clinical practice to describe metabolic acidoses which are associated with the accumulation of ketone bodies in the serum.

The most common being diabetic ketoacidosis. Other causes and mechanisms of ketosis and ketoacidosis[5] are listed in Table 1. There are three major ketone bodies, acetoacetic acid is the only true ketoacid. The more dominant acid in patients with ketoacidosis is beta-hydroxybutyric acid (elevated in our patient), which results from the reduction of acetoacetic acid by NADH. Beta-hydroxybutyric acid is a hydroxyacid, not a true ketoacid. Acetone, which is formed from the decarboxylation of acetic acid, is a true ketone but **not** an acid. Hepatic generation of ketone bodies is usually stimulated by the combination of low insulin levels and high glucagon levels. A good example of this would be fasting where a low insulin/ glucagon ratio is seen.

Table 1.

Causes of Ketoacidosis	**Mechanism of Acidosis**
1. Diabetic Ketoacidosis	Insulin Deficiency and reduced oxaloacetate→ ketogenesis
2. Starvation Ketosis	Depleted body glycogen stores and low insulin: glucagon ratio → hepatic ketone production
3. Alcoholic Ketoacidosis	Poor nutrition, ethanol metabolism and metabolic stress →depletion of protein and hepatic glycogen→ketogenesis
4. Salicylate Poisoning (Mixed Acidosis)	a. Uncoupling of mitochondrial oxidative phosphorylation→lactate formation. **b.** Salicylate→fatty acid breakdown→ketosis
5. Inborn Errors of Metabolism	Recessively inherited disorders→ impaired metabolism and ketone production e.g. Methylmalonic Aciduria
6. Bovine Ketosis/Lactation Ketosis	High glucose utilization during lactation→depletion of hepatic glycogen stores by gluconeogenesis→low insulin:glucgon ratio→ketogenesis

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