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A SELF-TEST ON A CLINICAL CASE

A 58-year-old woman with mental status changes

A 58-YEAR-OLD WHITE WOMAN presents to the emergency department stating that for the past 8 weeks she has had transient episodes of confusion, slurred speech, and unsteady gait, and that more recently she has had impairment of her short-term memory along with visual and auditory hallucinations, which include seeing and hearing deceased family members.

During the medical and surgical history, she reports having had a generalized anxiety disorder in the past and having undergone intestinal bypass surgery for obesity in 1975. She says that she has had chronic diarrhea since the surgery, but that the episodes of diarrhea had become a bit more frequent since her neuropsychiatric symptoms began 8 weeks ago.

She reports no fevers, chills, headaches, lightheadedness, or change in vision, and she has not had nausea, vomiting, abdominal pain, hematemesis, hematochezia, or melena. She has no cardiac, respiratory, or urinary symptoms. She is not taking any medications. She says she does not smoke, drink alcohol, or use illicit drugs. She has not recently changed her diet and has maintained a low-carbohydrate diet (approximately 60–70 g per day) for many years for weight control.

On examination, she is not in acute distress. Her vitals signs are temperature 36.5°C (97.7°F), blood pressure 125/80 mm Hg, heart rate 65 beats per minute, respiratory rate 15 per minute, and oxygen saturation 96% on room air. Her skin appears normal. Her head and neck show no obvious abnormalities, lymphadenopathy, or thyromegaly. The cardiopulmonary examination is normal. She has normal bowel sounds with mild epigastric tenderness but no guarding or rebound tenderness. Strength in the upper and lower extremities is 5 on a scale of 5. Sensation to light touch, pinprick, and vibration is intact. Reflexes, cranial nerve, and gait are also normal.

INITIAL LABORATORY TESTS PROVIDE A CLUE

A look at the patient's initial laboratory test results (TABLE 1) shows a low bicarbonate level,

TABLE 1

The patient's laboratory values on admission

TESTS	RESULTS	NORMAL RANGE
Sodium	141 mmol/L	132–148
Potassium	3.7 mmol/L	3.5–5.0
Chloride	110 mmol/L	98–111
Bicarbonate	16 mmol/L	23–32
Blood urea nitrogen	15 mg/dL	8–25
Creatinine	1.2 mg/dL	0.7–1.4
Glucose	87 mg/dL	65–100
Hemoglobin	11.9 g/dL	12–16
Hematocrit	36.8%	37–47%
White blood cells	5.5×10^9/L	4–11
Platelets	120×10^9/L	150–400
Alanine aminotransferase	26 U/L	0–45
Aspartate aminotransferase	21 U/L	7–40
Alkaline phosphatase	101 U/L	40–150
Bilirubin, total	0.8 mg/dL	0–1.5
Albumin	3.5 g/dL	3.5–5
Ethanol	Negative	

TABLE 2

Causes of metabolic acidosis

Elevated anion gap
Lactic acidosis
Ketoacidosis related to diabetes, starvation, alcohol abuse
Methanol, ethylene glycol, or aspirin ingestion
Chronic renal failure

Normal anion gap
Diarrhea
Renal tubular acidosis
Carbonic anhydrase inhibitors
Intestinal or ureteral diversion

which prompts us to calculate her anion gap. Using the formula *Anion gap = Na – (Cl + HCO_3)*, we calculate her anion gap as 15 mEq/L (normal 8–12 mEq/L), indicating high anion gap metabolic acidosis. The serum lactate 0.9 (0.9–2.0 mmol/L) and pyruvate 0.03 (0.03–0.08 mmol/L) levels are normal. The patient had previously been informed of a diagnosis of metabolic acidosis, but a cause had not been found despite investigations by other physicians.

She had intestinal bypass for obesity in 1975 and has had diarrhea since then

1 Which is likely the cause of her metabolic acidosis?

- ❑ Diarrhea
- ❑ Methanol ingestion
- ❑ Ethanol ingestion
- ❑ Salicylate overdose
- ❑ Lactic acidosis

A number of diseases can cause metabolic acidosis, usually via one of three mechanisms: increased acid generation, loss of bicarbonate, or diminished renal excretion of acid. The four most common types of high anion gap metabolic acidosis are lactic acidosis, ketoacidosis (secondary to diabetes mellitus, alcohol abuse, or starvation), toxins (including methanol, ethylene glycol, and salicylates), and renal failure. Since the anion gap reflects both measured and unmeasured cations and anions, an increase in the anion gap may be due to a decrease in unmeasured cations (ie, hypocalcemia) or to an increase in unmeasured anions (ie, accumulation of an organic anion) (TABLE 2).[1–3]

Diarrhea

Diarrhea can cause metabolic acidosis because intestinal secretions are alkaline (base concentration of 50–70 meq/L)[4] and is usually accompanied by hypokalemia, since the secretions are rich in potassium. The anion gap is usually normal; although bicarbonate is lost in the stool, the kidney compensates by reabsorbing NaCl to preserve extracellular fluid volume. Therefore, chloride is elevated, producing hyperchloremic acidosis. If diarrhea is severe enough to cause massive fluid losses, a high anion gap acidosis can develop. If left untreated, a high anion gap acidosis may develop secondary to hyperalbuminemia (due to hemoconcentration) and hypoperfusion (leading to lactic acidosis). In the latter scenario, rehydration with colloid fluids and alkali therapy can normalize the anion gap.[4–6]

Diarrhea is unlikely to be the cause in this patient, since her potassium level is within the normal range and since her laboratory tests show a high anion gap acidosis. In addition, she does not have severe diarrhea and she has no evidence of dehydration or volume depletion on clinical examination.

Methanol ingestion

Methanol ingestion is associated with the development of high anion gap metabolic acidosis with an associated osmolar gap. Serum osmolality is determined mainly by sodium, its concentrations, and concentrations of uncharged species such as glucose and blood urea nitrogen. Knowledge of the plasma concentration of these allows for an accurate calculation of serum osmolality that matches measured osmolality quite closely:

Calculated serum osmolality =
(2 × serum Na) + (serum glucose/18)
+ (blood urea nitrogen/2.8)

A significant difference between the measured and the calculated osmolality is noted when methanol or ethylene glycol is ingested, which increases the measured osmolality.

Methanol is metabolized by alcohol dehydrogenase to formaldehyde and then to formic acid. Formaldehyde has a very short half-life, while the metabolism of formic acid is very

slow. Therefore, formic acid accumulates and is responsible for the anion gap metabolic acidosis and damage to the optic nerve, retina, and basal ganglia.

Ethanol ingestion and salicylate overdose

Excessive ingestion of ethanol usually presents with an increased anion gap acidosis secondary to the introduction of organic acids into the circulation. In this case, the most common organic acid is the unmeasured anion B-hydroxybutyrate, which causes ketoacidosis.[7] There is also a mild degree of lactic acidosis with alcoholism due to lactate underutilization, secondary to impaired hepatic gluconeogenesis.

Deliberate or accidental ingestion of salicylates can produce a high anion gap acidosis, although early after the ingestion a respiratory alkalosis is usually the more pronounced acid-base disorder. The increase in anion gap is only partly from the unmeasured salicylate anion, which enters the central nervous system and leads to respiratory alkalosis and central nervous system toxicity. Increased keto acid and lactic acid levels have been reported in persons with salicylate overdose and are thought to account for the remainder of the anion gap.

Our patient has no history of alcohol or salicylate ingestion. Furthermore, her blood alcohol level is negative and she has no other signs of salicylate overdose, such as tachypnea.

Lactic acidosis

Lactic acidosis (associated with an elevated anion gap) occurs usually with accumulation of L-lactic acid, which is metabolized by L-lactate dehydrogenase. Lactate is produced by anaerobic metabolism resulting from impaired tissue oxygenation or impaired oxidative metabolism. The pathophysiology of lactic acidosis involves both the overproduction (anaerobic metabolism) and the impaired metabolism of lactate. Healthy people normally produce 15 to 20 mmol/kg of lactic acid per day, most of which is generated from glucose via the glycolytic pathway, metabolized by the liver, and cleared via the kidney.[8,9] Lactic acidosis develops as the plasma lactate concentration increases above 2 mmol/L (the normal lactate concentration is 0.9–2.0 mmol/L).

Our patient has had an increase in episodes of diarrhea. However, diarrhea usually causes a non-anion-gap acidosis, and she has no evidence of volume depletion. In addition, she has no history of diabetes or alcohol use. Therefore, the cause of her metabolic acidosis is likely lactic acidosis.

CASE CONTINUED

So far we have confirmed that the patient has a high anion gap metabolic acidosis (anion gap 15 mEq/L), with a serum lactate level of 0.9 (0.9–2.0 mmol/L) and a serum pyruvate of 0.03 (0.03–0.08 mmol/L), both of which are normal. Magnetic resonance imaging is ordered to further evaluate her mental status changes in the absence of a satisfactory explanation from the laboratory tests alone. Magnetic resonance imaging of the brain shows chronic small-vessel ischemic changes but no acute ischemic events.

2 Of the different types of lactic acidosis, which is most likely present in this patient in view of her normal serum lactate level?

- ❑ Type A
- ❑ Type B
- ❑ Type D

Diarrhea can cause metabolic acidosis with a normal anion gap

Type A lactic acidosis, which accounts for most cases, is due to impaired tissue oxygenation, as may occur in cardiac arrest, hypovolemia, or sepsis, or to impaired cellular metabolism. Type B is due to local areas of ischemia and is seen in alcoholism and in people with malignancy, and as a complication of highly active antiretroviral therapy for human immunodeficiency virus infection or of other medications, such as metformin.[10–13]

Type D is the most likely choice. It occurs mainly in patients with jejunoileal bypass or short-gut syndrome due to other causes. In type D, sugars (glucose and starch) reach the colon mainly undigested and are converted into D-lactic acid, which is absorbed into the systemic circulation but is not measured on routine testing for lactate levels.[11,14,15]

CASE CONTINUED

Because our patient has previously undergone intestinal bypass surgery, we suspect D-lactic acidosis and so we order a test of the D-lactate level, a special enzymatic assay that uses D-lactate dehydrogenase.[16,17] While awaiting the test results, we treat her with sodium bicarbonate tablets to neutralize the acidosis and metronidazole (Flagyl) to decrease the production of D-lactic acid by intestinal bacteria.

Her D-lactate level is 0.36 mmol/L, which is elevated (normal range 0.0–0.25 mmol/L), thus making the diagnosis of D-lactic acidosis very likely. It has been postulated that a higher D-lactate level is required for the diagnosis of this condition, but no clear-cut levels have been established owing to the rarity of the disorder.[7,10,14,18] Moreover, levels of D-lactate are known to fluctuate markedly with time in this condition. Nevertheless, in view of the clinical and laboratory findings, only D-type lactic acidosis could satisfactorily account for this patient's symptoms.

FACTORS CONTRIBUTING TO OVERPRODUCTION OF D-LACTIC ACID

Type D lactic acidosis is seen mainly in short-gut syndrome

Most sugars and starches are digested in the small intestine, and normally the colon is involved in the fermentation of fiber and resistant starch to organic acids.[18] In short-bowel syndrome secondary to small-bowel resection or jejunoileal bypass surgery, a larger than normal amount of carbohydrate is delivered to the colon. Malabsorbed carbohydrates are fermented directly in the colon to produce organic acids. Thus, the pH of the colon decreases and favors the growth of acid-resistant bacteria at the expense of the normal gut flora. Acid-producing gram-positive anaerobic bacteria (*Lactobacillus acidophilus, L fermenti, Streptococcus bovis*) produce D-lactate. High amounts of D-lactate are then absorbed into the circulation, resulting in an elevated concentration in the blood (**FIGURE 1**).[11]

3 What are the most common neurologic symptoms of patients who present with D-lactic acidosis?

- ❑ Altered mental status
- ❑ Headaches
- ❑ Blurred vision
- ❑ Ataxia
- ❑ Hallucinations

Neurologic abnormalities associated with D-lactic acidosis include some form of altered mental status, such as confusion, cerebellar ataxia, slurred speech, or loss of memory.[11,14,15] However, higher concentrations of D-lactate do not always produce neurologic symptoms.

Patients with short-bowel syndrome can have chronically elevated serum concentrations of D-lactate, but these concentrations may not be sufficient to induce symptoms.[16] Moreover, the neurologic examination can be completely normal.[10,17,19]

The reasons for the neurologic symptoms are not completely understood. Some postulate that D-lactate is itself toxic to the brain due to lack of D2-hydroxyacid dehydrogenase needed for metabolism.[20] Another theory is that high levels of D-lactic acid may alter intraneuronal pH, which would interfere with the pyruvate dehydrogenase complex and therefore decrease production of acetyl coenzyme A and adenosine triphospate. This chain of events would lead to an outcome of altered neurotransmitter production, resulting in central nervous system symptoms.[20–22]

4 What is the appropriate treatment for D-lactic acidosis?

- ❑ Intravenous hydration and observation
- ❑ Antibiotics
- ❑ Hemodialysis
- ❑ Reversal of intestinal bypass
- ❑ Low-carbohydrate diet
- ❑ All of the above

All of the above are appropriate, depending on the patient's condition.

D-lactic acidosis can often have a transient and self-limited course. Therefore, the patient should first receive intravenous hydration. Treatment also includes giving sodium bicarbonate to correct the acidemia. The oral antimicrobial agents metronidazole, neomycin, and vancomycin are often used to decrease the number of organisms producing D-lactate.[11,14,15] Caution must be used when using certain antibiotics, however, as they can

Pathogenesis and treatment of D-lactic acidosis

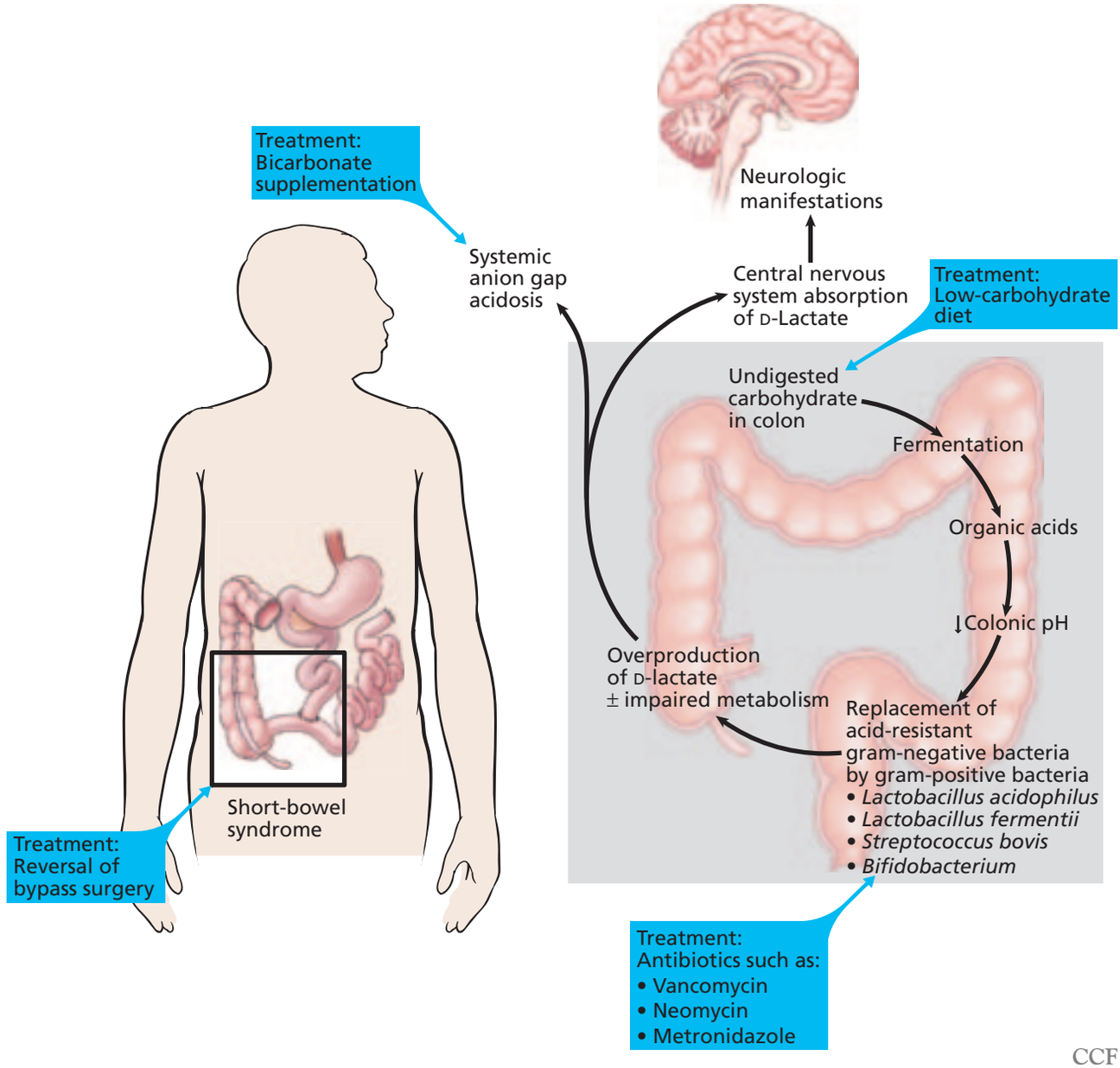

FIGURE 1. Pathogenesis and treatment of D-lactic acidosis

lead to selective growth of bacteria that produce D-lactate. A low-carbohydrate diet also is helpful in reducing the carbohydrate load to the colon.[23,24] Other plausible treatment options include insulin to diminish fatty acid levels and enhance D-lactate clearance, and, if the patient's condition is more critical, hemodialysis is effective.[14,16] Reversal of the cause is also a plausible option (in case of jejunoileal bypass) in certain patients.[18]

CASE CONCLUDED

Upon discharge, the patient has a normal anion gap and has not had any more episodes of the mental status changes that had brought

her to the hospital.

D-lactic acidosis should be considered in patients with a history of abdominal surgery resulting in short-bowel syndrome or malabsorption and who present with a high anion gap metabolic acidosis and neuropsychiatric manifestations. Our patient was diagnosed with anion gap metabolic acidosis by other physicians, but the cause was not discovered until a more elaborate history was obtained. As we described, symptoms can be considerably delayed, and physicians should be aware of such clinical presentations, since a remote surgical history may be the key to diagnosing a patient's medical condition. This is even more relevant as more and more patients have gastrointestinal bypass surgery for obesity and can present many years later. Interestingly, to our knowledge, the onset of symptoms approximately 30 years after intestinal surgery has not been reported previously. ■

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