CASES

D-lactic acidosis and ataxia in a man with Crohn disease

Paul D. James MD MSc, David Black MD, Ayelet Kuper MD DPhil, Fred Saibil MD

Previously published at www.cmaj.ca

A 49-year-old man presented to the emergency department with an eight-hour history of unsteady gait, impaired concentration, difficulty speaking and blurry vision, which had developed over the previous seven hours. During the preceding two days, he had been excessively thirsty and drank large amounts of water, cola and a "sports drink." He had eaten a large portion of rice with dinner the evening before presentation. On the day he presented, he had awoken in the morning feeling dizzy. As he was leaving for work, he had experienced difficulty using his keys and turning doorknobs.

The patient's medical history included Crohn disease and two major small-bowel resections at 33 and 35 years of age that had left about one metre of small intestine. He had undergone an esophageal bougienage three weeks earlier for a stricture related to Crohn disease. After the bougienage, the patient had regained his ability to consume solids and dramatically increased his caloric intake to regain weight. His diet consisted mainly of fast food, candy bars and soft drinks.

The patient reported that he did not smoke, consume substantial amounts of alcohol or have any drug allergies. On a daily basis, he took prednisone 20 mg, loperamide 2–4 mg, vitamin B_{12} and multivitamins. Except for the addition of prednisone for the Crohn-related stricture, his regimen of medications had not changed during the past year. He had experienced no changes in his usual Crohn symptoms.

Key points

- When common causes of mixed, normal or large anion gap metabolic acidosis have been ruled out, a comprehensive review of less common causes should be considered.
- D-lactic acidosis should be considered in patients at risk for short-bowel syndrome who have new-onset gait ataxia, cerebellar dysfunction and metabolic acidosis with a large anion gap.
- Treatment consists mainly of intravenous fluid resuscitation and poorly absorbed oral antibiotics. Prevention strategies include a low-carbohydrate diet, maintenance of hydration and avoidance of simple sugars.

Table 1: Laboratory values on admission

Laboratory investigation	Result	Normal range, mmol/L*
Sodium	139.0	135–147
Potassium	4.3	3.5–5.0
Chloride	107.0	95–107
Carbon dioxide	10.0	22–30
Random glucose	7.1	4.0–8.0
Albumin	39.0	35–50 g/L
Osmolality	292.0	280–300 mmol/kg
Urea	2.3	3.0–7.0
Arterial pH	7.21	7.35–7.45
Arterial partial pressure of carbon dioxide (pCO_2)	23.0	35–45 mm Hg
Arterial partial pressure of oxygen (pO_2)	119.0	80–100 mm Hg
Arterial bicarbonate	9.0	22–26

*Unless otherwise indicated.

On clinical examination, the patient was alert, oriented and not in distress. His vital signs were normal and he had no significant postural changes. Other than mild vertical and horizontal nystagmus, the results of cranial nerve testing were normal. The patient had truncal ataxia and notable dysmetria on finger-nose testing. He had an unsteady, wide-based gait and could not tolerate walking more than five steps. Rapid alternating movements and heel-shin tests were normal. His strength and reflexes, and the results of sensory testing, were normal. The rest of the clinical examination was unremarkable except for midline abdominal surgical scars.

Initial laboratory investigations are presented in Table 1 and include a serum carbon dioxide level of 10 mmol/L with an anion gap of 22 mEq/L. Complete blood count, creatinine, coagulation studies, liver enzymes and urinalysis were within normal limits. Arterial blood gas analysis showed a pH of 7.21, partial pressure of carbon dioxide (pCO_2) of 23, partial pressure of oxygen (pO_2) of 119 and HCO_3^- of 9. Serum lac-

From the Department of Internal Medicine (James), Faculty of Medicine, University of Toronto; and the Division of Gastroenterology (Black, Saibil, Kuper), Department of Internal Medicine, and Wilson Centre for Research in Education (Kuper), Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ont.

CMAJ 2010. DOI:10.1503/cmaj.090009

DOI:10.1503/cmaj.090009

tates and osmolal gap were normal. Screens for serum salicylates, acetaminophen, alcohol and ketones were negative. A computed tomography scan and magnetic resonance imaging of the patient's brain were also normal.

The patient was admitted for further investigation and given 2 L of isotonic saline over eight hours for suspected mild hypovolemia. The next morning, his anion gap was normal. The only neurologic symptom that persisted was a sensation of gait imbalance. On re-examination, all abnormal findings had disappeared except for the ataxia, which was markedly improved. Within 24 hours, the patient's symptoms had resolved.

A review of the literature on causes of anion-gap acidosis raised the possibility of D-lactatemia, particularly given the patient's history of multiple small-bowel resections. His first blood sample from the emergency department was refrigerated and sent to a specialized research laboratory for a D-lactate assay.

The patient was discharged with a provisional diagnosis of D-lactic acidosis. He was advised to consume a low-carbohydrate diet and was given a prescription for metronidazole to be started promptly in the event of recurrence of his neurologic symptoms. This poorly absorbed antibiotic is effective in reducing levels of D-lactate-producing bacteria.

The result of the D-lactate assay came back several days later and was 8 mmol/L (normal < 1.0 mmol/L).

Discussion

Metabolic acidosis with an elevated anion gap has a limited differential diagnosis (Box 1).[1,4–6] The laboratory tests investigating these typical causes were negative in our patient. D-lactic acidosis is a much rarer cause of metabolic acidosis with an elevated anion gap. Its presence is suggested by elevation of the anion gap in patients with shortened small bowels when other causes have been excluded (Table 2).

The presence of D-lactic acidosis can be confirmed by a serum assay showing a higher than normal D-lactate level. A level greater than 3 mmol/L is diagnostic for this condition.[1] Measurement of D-lactate, however, is not available routinely in most hospital laboratories. Urinary D-lactate assays may be faster, easier to use and more sensitive than serologic assays.[2,3]

Association with short-gut syndrome

Various mechanisms have been proposed to describe the association between D-lactic acidosis and short-gut syndrome. Decreased surface area of the small bowel, as well as inflammation associated with excess bacteria, increase the risk that some carbohydrates may not be absorbed by the small intestine and thus pass undigested into the colon. There, they may serve as substrates for D-lactate-producing bacteria, such as *Lactobacillus*, *Streptococcus*, *Bifidobacterium* and *Eubacterium*. Growth of these bacteria is favoured in conditions of low luminal pH, which may be enhanced by insufficient neutralization of gastric acid.[4]

The anatomic lesions associated with bowel resections and reductions in bowel motility can provide colonic bacteria with an opportunity to migrate into the small intestine and metabolize carbohydrates before they are absorbed. Excess ingestion of carbohydrates, particularly those that are poorly broken down or absorbed, can then lead to high levels of colonic D-lactic acid.[5]

High-fructose corn syrup has been added increasingly to commercially available sweetened drinks over the past 40 years. Fructose that is joined with glucose in the form of a sucrose disaccharide is well absorbed by glucose transporters. However, because of a lack of fructose-specific intestinal transporters, the absorption of fructose is limited when it is found in mixtures with excess glucose. This limited absorption results in elevated luminal sugar substrates for D-lactic acid production.[6]

Various dietary sources of D-lactate exist, including sour milk, molasses, and certain fruits and vegetables. Clinical investigations into the efficiency with which D-lactate is metabolized have been contradictory. Some studies have found that it is readily metabolized to pyruvate by D-lactate dehydrogenase in the liver and kidneys[7] at a rate similar to the metabolism of L-lactate.[8] Other studies have shown that it is metabolized more

Box 1: Differential diagnoses for large and normal anion gap metabolic acidoses[1,4-6]

Common causes of metabolic acidosis with a large anion gap

Production of endogenous acids:
- Ketoacidosis (e.g., associated with diabetes, alcoholism, toxicity, starvation)
- Renal failure
- Lactic acidosis (e.g., caused by poor tissue oxygenation, decreased renal clearance, toxins)

Ingestion of exogenous acids:
- Toxic alcohols (e.g. ethylene glycol and methanol)
- Acetylsalicylic acid
- Paraldehyde

Ingestion of other potential toxins:
- Phenformin
- Iron
- Isoniazid
- Acetaminophen

Common causes of metabolic acidosis with a normal anion gap

Gastrointestinal losses of bicarbonate:
- Diarrhea
- Pancreatic fistula
- High-volume drainage of gastrointestinal tube

Renal losses of bicarbonate:
- Proximal renal tubular acidosis

Impairment of renal hydrogen secretion:
- Distal renal tubular acidosis
- Hypoaldosteronism

Ingestion of potential toxins:
- Toluene
- Carbonic anhydrase inhibitors
- Cholestyramine

Dilutional:
- Rapid infusion of intravenous fluids that do not contain bicarbonate

slowly because of lower abundance of specific metabolizing enzymes for D-lactate and slower renal clearance.[9]

Neurologic findings

The clinical manifestations of D-lactic acidosis are listed in Box 2[1,4,10] and include altered mental status and cerebellar ataxia. The cause of these neurologic abnormalities is debated. A reduction in serum pH alone is insufficient to explain such manifestations, given that acidosis of comparable severity from other causes does not always result in this presentation. Various theories have been advanced, including suggestions that low pH may affect intraneural metabolism of L-lactate, which is the preferred substrate of nervous aerobic metabolism,[11] or may inhibit central and peripheral neurotransmitter production.[4,12] The accumulation of D-lactate in brain tissue because of naturally low levels of D-lactate dehydrogenase has also been hypothesized.[11]

These theories are not supported by a study showing that infusion of D-lactate into healthy volunteers to a serum concentration of 6 mmol/L did not cause neurologic symptoms.[9] This finding suggests the presence of other mediators associated with D-lactate.[1,5,9] However, infusing D-lactate into peripheral venous blood may not reproduce the clinical presentation associated with D-lactic acidosis because D-lactate absorbed from the colon passes through the portal circulation and into the liver before being released into the systemic circulation.

Treatment

Although treatment of D-lactic acidosis includes intravenous fluid resuscitation to promote renal excretion of D-lactic acid, no evidence exists to support this intervention in euvolemic patients.[10] Poorly absorbed oral antibiotics (e.g., metronidazole, neomycin and vancomycin) are effective in reducing lev-

Table 2: Steps involved in determining the cause of metabolic acidosis

Step	In our patient
1. Calculate the anion gap	
The anion gap is the difference between the measured serum cations (i.e., plasma sodium) and serum anions (i.e., chloride and bicarbonate), or $Na^+ – (Cl^- + HCO_3^-)$. The normal anion gap is equal to 12 ± 2 mEq/L. If the patient has hypoalbuminemia, the result needs to be corrected. The normal anion gap corrected for hypoalbuminemia is equal to the anion gap + [(44 – serum albumin) × 0.25].	Results of testing for arterial blood gas (pH = 7.21, pCO_2 = 23 and HCO_3^- = 9) suggested a metabolic acidosis with respiratory compensation. Anion gap = $Na^+ – (Cl^- + HCO_3^-)$ = 139 – (107 + 9) = 23, which is consistent with metabolic acidosis with a large anion gap.
2. Determine whether the type of acidosis is mixed or non-anion gap	
Metabolic acidosis with a normal anion gap is associated with loss of bicarbonate or failure to excrete hydrogen ions from the body (Box 1). To determine if there is a mixed anion gap or non-anion gap acidosis, compare the difference in the delta bicarbonate to the delta anion gap. A concomitant non-anion gap may be present if (normal HCO_3^- – measured HCO_3^-) is greater than (normal anion gap – calculated anion gap).	Delta bicarbonate was 24 – 10 = 14. The delta anion gap was 12 ± 2 –23 = -9 to -13. The difference in HCO_3^- from the expected value was 14. The difference in the anion gap from the expected value was -9 to -13. Because only a small discrepancy was observed, a pure large anion gap metabolic acidosis was diagnosed.
3. Determine whether the acidosis is caused by endogenous acids or ingestion of exogenous acids	
A large anion gap metabolic acidosis suggests the addition of exogenous or endogenously generated acids. To determine whether ethanol, methanol or ethylene glycol ingestion may have contributed to an anion gap metabolic acidosis, determine the osmolal gap. The osmolal gap is equal to (measured osmolality – calculated serum osmolality). Calculated serum osmolality = 2 × Na^+ + glucose + urea If the osmolal gap is greater than 10, ingestion of methanol or ethylene glycol should be considered a possible cause.	The osmolal gap was equal to (measured osmolality – calculated osmolality), or 292 – (2 × 139 + 7.1 + 2.3) = 4.6, which was not large enough to consider methanol or ethylene glycol ingestion as a cause. Preliminary screening for the most common causes of a large anion gap metabolic acidosis showed a negative toxicology screen for salicylates and ethanol. Serum lactate, glucose, creatinine and ketones were also normal. Based on clinical suspicion, a serum D-lactate assay was eventually ordered, which was positive.

Box 2: Clinical manifestations of D-lactic acidosis[1,4,10]

Altered mental status
- Disorientation
- Decreased level of consciousness
- Irritability
- Coma

Cerebellar signs
- Ataxia
- Dysarthria
- Gait disturbance
- Impaired motor coordination
- Nystagmus

Weakness

Blurred vision

Psychosis

els of D-lactate-producing bacteria.[10] Use of sodium bicarbonate to treat acidemia has not been consistently shown effective, and has adverse effects (e.g., volume overload, alkalemia, hypernatremia) that should be considered before it is administered.[13,14] In a patient with a critical level of D-lactate that may be life-threatening, acute administration of sodium bicarbonate followed by hemodialysis may be indicated.[15]

With treatment, the symptoms associated with D-lactic acidosis tend to have a limited course and typically resolve within 72 hours of onset, possibly owing to efficient hepatic metabolism and renal excretion.[4,8]

Prevention

Prevention of D-lactic acidosis begins with reduced consumption of substrates that promote the proliferation of acid-resistant colonic bacteria in patients with shortened small bowels. Therefore, a diet low in carbohydrates, including avoidance of sweetened beverages, is important. Immediate treatment with antibiotics when early symptoms (e.g., disorientation and dysarthria) are detected can avoid progression to the full spectrum of neurologic abnormalities.[4,12]

Competing interests: None declared.

Acknowledgement: The authors thank Dr. Mitchel Halperin for his helpful insight.

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Correspondence to: *Dr. Paul D. James, Faculty of Medicine, University of Toronto, 190 Elizabeth St., Toronto ON M5G 2C4; paul.james@utoronto.ca*

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