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Case Report

CASE REPORT

Common, yet elusive: a case of severe anion gap acidosis

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Abstract

Acid–base disturbances are common occurrence in hospitalized patients with life threatening complications. 5-oxoproline has been increasingly recognized as cause of high anion gap metabolic acidosis (AGMA) in association with chronic acetaminophen use. However, laboratory workup for it are not widely available. We report case of 56-year-old female with severe AGMA not attributable to ketoacidosis, lactic acidosis or toxic ingestion. History was significant for chronic acetaminophen use, and laboratory workup negative for all frequent causes of AGMA. Given history and clinical presentation, our suspicion for 5-oxoproline toxicity was high. Our patient required emergent hemodialysis and subsequently improved clinically. With an increasing awareness of the uncommon causes of high AGMA, tests should be more readily available to detect their presence. Physicians should be more vigilant of underdiagnosed causes of AGMA if the presentation and laboratory values do not reflect a common cause, as definitive treatment may vary based on the offending agent.

INTRODUCTION

High anion gap metabolic acidosis (AGMA) is a frequently observed acid–base disturbance seen in hospitalized patients. Common causes include diabetic, alcoholic and starvation ketoacidosis, lactic acidosis, renal failure or ingestion of salicylate, methanol, ethylene glycol and propylene glycol. There have been a few case reports in the recent years describing accumulation of organic acids such as pyroglutamic acid (5-oxoproline) in the setting of chronic acetaminophen use or D-lactate in a patient with short gut syndrome as the culprit for AGMA. We report a case of 56-year-old female with high AGMA of unknown etiology.

CASE VIGNETTE

A 56-year-old African–American female with a history of chronic back pain presented to the emergency department with epigastric pain and nausea for 2 days. Her vitals were stable on presentation and examination was unremarkable, but her laboratory workup revealed severe AGMA with a gap of 35 mmol/l, bicarbonate of 5 mmol/l and pH of 7.00.

On further questioning, she admitted to being a social drinker, but her last drink was 2 glasses of gin 2 days prior to arrival. She denied any toxic substance ingestion, including anti-freeze, wood alcohol or aspirin, and only admitted to chronic use of acetaminophen, ~1.5 g/day. Her glucose, ketone and L-lactic acid level were normal. Acetaminophen, salicylate and ethanol levels were undetectable. Her kidney function was preserved with creatinine 1 mg/dl and blood urea nitrogen 13 mg/dl. She had an osmolar gap of 22 mOsm/kg. Her ethylene glycol, methanol and propylene glycol levels were undetectable.

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She received intravenous fluids and bicarbonate infusion in the emergency department with no significant improvement in her acidosis. After discussion with nephrologist, the patient received emergent hemodialysis for the profound acidemia. Subsequent laboratory workup after hemodialysis showed normal venous pH of 7.37, anion gap of 22 mmol/l and bicarbonate level of 14 mmol/l. Since the common causes were ruled out, the foremost differential was pyroglutamic acid toxicity in the setting of chronic acetaminophen use. Unfortunately, urine testing for pyroglutamic acid and D-lactic acid were not available in the hospital laboratory. The patient was advised to refrain from chronic acetaminophen use and was discharged home in 3 days and advised follow-up within a week.

DISCUSSION

Metabolic acidosis is a commonly observed acid–base disturbance in hospitalized patients. While old mnemonics like 'MUDPILES' are popular, with the additional newly identified causes, Mehta *et al*. [1] described a new mnemonic of the 21st century: GOLD MARK to enumerate the causes of high AGMA. It includes glycols (ethylene and propylene), oxoproline, L-Lactate, D-Lactate, methanol, aspirin, renal failure and ketoacidosis.

First described in 1989, 5-oxoproline has been increasingly recognized as a cause of high AGMA. The propensity to develop this toxicity following acetaminophen exposure might be genetically determined, and there appears to be a propensity in women [2, 3]. 5-oxoproline is a product of the gamma-glutamyl cycle; a lack of glutathione leads to accumulation of glutamylcysteine and its conversion to 5-oxoproline through an alternate pathway [4]. There is some albeit weak evidence supporting the role of *N*-acetyl cysteine in treating 5-oxoprolinemia; Fenves *et al*. [3] support its supplementation to increase glutathione synthesis. Definitive treatment, however, depends on recognizing its presence and cessation of acetaminophen intake.

Another under recognized cause of AGMA is D-lactic acidosis, which occurs in patients with malabsorption after short bowel syndrome or bariatric surgery [5] as a product of bacterial carbohydrate metabolism. The commonly measured lactic acid in laboratory usually only reflects the L-lactic acid.

Our patient was admitted with high AGMA, with the common causes ruled out. With the history of chronic acetaminophen use, our suspicion for 5-oxoproline toxicity was high. Due to non-availability of the test in hospital laboratory, we were unable to prove the etiology of the metabolic acidosis in our patient.

CONCLUSION

High AGMA is usually associated with known common conditions such as diabetic, alcoholic, starvation ketoacidosis and lactic acidosis, though rarely it may be secondary to accumulation of urine organic acids such as pyroglutamic acid or D-lactic acid. With an increasing awareness of the uncommon causes of high AGMA, tests should be more readily available to detect their presence. Also a clinician should be suspicious for these underdiagnosed causes if the presentation and laboratory values do not reflect a common cause.

CONFLICT OF INTEREST STATEMENT

None declared.

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