Rare disease

Chronic acetaminophen ingestion resulting in severe anion gap metabolic acidosis secondary to 5-oxoproline accumulation: an under diagnosed phenomenon

L. Morgan Nordstrom O'Brien,¹ Michael Hooper,² Mark Flemmer,¹ Paul Ellis Marik²

¹Department of Medicine, Eastern Virginia Medical School, Norfolk, Virginia, USA;

²Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical school, Norfolk, Virginia, USA

Correspondence to Dr Paul Ellis Marik, marikpe@evms.edu

Summary

Anion gap metabolic acidosis is commonly caused by lactic acidosis, ketoacidosis, and ingestion of methanol, salicylates, ethylene glycol or accumulation of organic/inorganic acids. However, rare causes of metabolic acidosis from enzyme defects, such as disturbances in the γ -glutamyl cycle, are being reported in higher frequencies in the adult population. Such disturbances cause an accumulation of 5-oxoproline and ultimately an anion gap metabolic acidosis. These disturbances are often associated with acetaminophen in the setting of certain risk factors such as sepsis, malnutrition, liver disease, female gender, pregnancy or renal failure.

BACKGROUND

5-oxoproline accumulation should be considered in cases of severe anion gap metabolic acidosis, particularly in patients with recent paracetamol use in combination with sepsis, malnutrition, liver disease, female gender, pregnancy or renal failure. Prompt treatment with intravenous n-acetylcysteine is recommended in these patients.

CASE PRESENTATION

A 54-year-old cachectic woman presented with altered mental status and a history of gastric bypass 6 years previously which was revised 4 years ago, hepatic steatosis and alcoholism. The patient presented severely malnourished; she was 1.5 m tall and weighed 36.2 kg with a body mass index 16.16 kg/m². Unfortunately, prior surgical details were unavailable because the patient had never been to our facility prior and she was non-compliant with routine follow-up. On admission, she was hypotensive and minimally responsive. Labs revealed an elevation of transaminases (aspartate aminotransferase 332 U/l, alanine aminotransferase 365 U/l, normal values are 10–37 and 5–40 U/l, respectively), hyperammonemia (445 μ mol/l, normal values ranging 23–47 μ mol/l), and a severe anion gap metabolic acidosis; pH 7.10, bicarbonate 7 mmol/L, anion gap 28 (normal pH 7.35–7.45, bicarbonate 21–27 mmol/l). The anion gap equation employed was $\text{Na} - (\text{Cl} + \text{HCO}_3^-)$ with normal ranges of 10–12. Her blood urea nitrogen was 1.07 mmol/l (normal 2.5–6.43 mmol/l) and her creatinine was 70 μ mol/l (normal 60–110 μ mol/l). Salicylate, methanol and ethanol were not detected. Lactate was 5.2 mmol/l (normal <2 mmol/l). There were no signs of infection; she was afebrile (36.7°C) with a normal white blood cell. Serum procalcitonin, a sepsis biomarker, was normal (<0.25 ng/ml). C reactive protein was not measured. Given her critical

illness, she was initially treated with empiric antibiotics. Ultimately, blood and urine cultures were negative. After fluid resuscitation, her lactate improved, but her anion gap metabolic acidosis persisted (pH 7.05). Her paracetamol level was 24 μ g/ml (normal therapeutic ranges in our laboratory is 10–30 μ g/ml). Despite supportive care and intravenous n-acetylcysteine, the patient died. Her severe malnourished state, large anion gap acidosis and elevation in paracetamol provoked an investigation into defects of the γ -glutamyl cycle. Ultimately, results revealed increased 5-oxoproline levels at >2000 mmol/mol creatinine in urine (normal <100 mmol/mol creatinine in urine).

TREATMENT

Prompt treatment with intravenous n-acetylcysteine is recommended in these patients.

OUTCOME AND FOLLOW-UP

The patient unfortunately died as a result of multi-organ failure.

DISCUSSION

The γ -glutamyl cycle produces 5-oxoproline during the synthesis of glutathione. Glutathione scavenges free radicals, detoxifies, is a component of redox reactions and is involved in amino acid transport. Accumulation in 5-oxoproline can occur as a result of glutathione synthetase deficiency, 5-oxoprolinase deficiency, and/or decreased feed-back inhibition resulting from low glutathione^{1–8} (figure 1).

Disturbances in the γ -glutamyl cycle can occur via inherited or acquired defects. Genetic disease can result in glutathione synthetase deficiency or 5-oxoprolinase deficiency.^{5–7} Interestingly, 1/10 000 people are heterozygous for glutathione synthetase deficiency and may

Figure 1 The γ -glutamyl pathway. Note negative inhibition of glutathione on γ -glutamyl cysteine synthetase and various risks that decrease glutathione concentrations.

be more prone to 5-oxoproline elevations with certain risk factors.⁹ Acquired defects in the γ -glutamyl cycle are often due to decreased glutathione body stores. Several publications have attributed decreased body glutathione levels to paracetamol use, even at therapeutic levels, when combined with malnutrition, liver disease, sepsis, vigabatrin use, artificial feeds and pregnancy.^{1–6 10} Some studies found elevations in 5-oxoproline levels in burn patients and Stevens Johnson Syndrome.¹¹ Paracetamol alone is an unlikely cause of 5-oxoproline induced anion gap acidosis without the aforementioned risk factors. One case involved 5-oxoprolinuria in a pregnant, septic patient after paracetamol ingestion. After delivery and resolution of sepsis, the patient was given a paracetamol challenge and there was no evidence of 5-oxoprolinuria.¹⁰ Female gender is also a likely risk factor for 5-oxoproline accumulation. Research performed in a murine model demonstrates sex-related glutathione-S-transferase isoenzymes, which could play a role in the development of 5-oxoproline accumulation.¹² However, it is important to note that 5-oxoproline levels are not a routinely available laboratory test. Thus we highly recommend contact with the laboratory to provide an appropriate timeframe for obtaining results.

Our patient had numerous risk factors promoting 5-oxoproline accumulation. She was a malnourished female alcoholic with hepatic steatosis who had previously has gastric bypass surgery and was abusing paracetamol. The increased lactic acid contributed to her acidosis, but was not sufficiently elevated to explain her severe anion gap acidosis. Anion gap acidosis has been reported from paracetamol elevations, but is rare, even in high amounts.⁷

Based on our experience and review of the available literature, we propose that 5-oxoproline accumulation should be considered as an aetiology in cases of severe anion gap metabolic acidosis. A history of paracetamol use in combination with malnutrition, liver disease, sepsis, female gender, pregnancy or renal failure should heighten suspicion. Prompt treatment with intravenous n-acetylcysteine is recommended in these patients.

Learning points

- 5-oxoproline accumulation should be considered in cases of severe anion gap metabolic acidosis.
- 5-oxoproline accumulation should be higher on the differential diagnosis in patients with recent paracetamol use in combination with sepsis, malnutrition, liver disease, female gender, pregnancy or renal failure.
- Prompt treatment with n-acetylcysteine is recommended in these patients.

Competing interests None.

Patient consent Obtained.

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