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CASE REPORT

5-Oxoproline as a cause of high anion gap metabolic acidosis: an uncommon cause with common risk factors

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ABSTRACT

High anion gap metabolic acidosis might be caused by 5-oxoproline (pyroglutamic acid). As it is very easy to treat, it might be worth drawing attention to this uncommon and probably often overlooked diagnosis. We present three cases of high anion gap metabolic acidosis due to 5-oxoproline seen within a period of six months.

KEYWORDS

Acidosis, high anion gap, oxoproline

CASE REPORTS

Case 1

A 72-year-old woman was treated with flucloxacillin (8 g/day) and lavage for septic arthritis of the right shoulder caused by *S. aureus*. Acetaminophen 4 g/day was prescribed to relieve the pain. She had documented osteoarthritis, frequent urinary tract infections and hypertension-induced renal failure. She was recovering when around the 10th day of treatment her condition started to deteriorate. Within a few days her breathing was laboured (Kussmaul breathing) and her consciousness became diminished (E3M5V4). Blood pressure (116/70 mmHg), pulse (81 beats/min) and temperature (36°C) were normal. Her renal function (Cockcroft-Gault clearance of 20 ml/min) was stable, and the cholestatic liver enzymes were slightly elevated (alkaline phosphatase (ALP) 191 U/l, gamma-glutamyl transferase (γGT) 117 U/l). The arterial blood gas analysis showed a pH of 7.12, a pCo_2 of 11 mmHg (1.47 kPa), a bicarbonate of 3.5 mmol/l, a base excess of -25 and a pO_2 of 175 mmHg (23.3 kPa) with oxygen. The anion gap was 30.75 mEq/l (corrected for serum albumin of 15 g/l). The serum lactate was repeatedly normal (0.7 mmol/l) and no ketones could be demonstrated in the urine. Ingestion of a substance such as ethylene glycol, methanol or salicylate was very unlikely. The acetaminophen level in the blood was therapeutic (3.2 mg/l). Although her body mass index (BMI) was 27 kg/m^2 she was malnourished. She was not artificially fed. A rapid Google search led us to the probable diagnosis of 5-oxoproline as a cause of this high anion gap metabolic acidosis in this malnourished patient with renal and lever insufficiency, who was taking acetaminophen and flucloxacillin. Acetaminophen was stopped and flucloxacillin was replaced by clindamycin. We treated her with bicarbonate (8.4%) and acetylcysteine (600 mg/8 hours). Her general condition improved rapidly. By gas chromatography-mass spectrometry[4,13] we demonstrated a highly elevated 5-oxoproline in urine (16,623 µmol /mmol creatinine (normal <100 µmol /mmol creatinine))[7,11] and plasma (6573 µmol/l (normal 15 µmol/l)). Two weeks later 5-oxoproline was undetectable in urine.

Case 2

A 56-year-old HIV-positive woman came to the outpatient clinic because of shortness of breath. She was treated with antiretroviral therapy (didanosine, lamivudine and efavirenz) for HIV (undetectable viral load and CD4 of 430/µl). In the past she had developed renal failure probably due to tenofovir, which was replaced by didanosine. A week ago she was treated for a urinary tract infection due to *E. coli* with norfloxacin (400 mg twice daily). She used alcohol and methadone chronically and had been taking acetaminophen 2 g/day since the urinary tract infection. The physical examination was unremarkable, except for

a weight of 47 kg and some shortness of breath while undressing. Capillary blood gas analysis showed a pH of 7.20, pCo_2 of 27 mmHg (3.6 kPa), and a bicarbonate of 10 mmol/l. We calculated an anion gap of 28 mEq/l (corrected for serum albumin of 31 g/l). Lactic acidosis caused by didanosine was suspected but the serum lactate was repeatedly normal (1.3 mmol/l). No ketones could be demonstrated in the urine. The serum creatinine had increased to 155 µmol/l (Cockcroft-Gault clearance of 27 ml/min), the cholestatic liver enzymes were elevated (ALP 382 U/l, γGT 534 u/l) and the osmolal gap was 0.9 mOsm/kg. The acetaminophen level was therapeutic (12 mg/l). Our experience with the first case made us think of 5-oxoproline as a cause of this high anion gap metabolic acidosis due to the combination of acetaminophen, malnourishment, renal failure and alcohol abuse. She recovered after discontinuation of acetaminophen. Again we demonstrated a high 5-oxoproline in plasma (2292 µmol/l) and urine (4184 µmol /mmol creatinine) which returned to normal.

Case 3

A 79-year-old woman with chronic obstructive pulmonary disease (COPD) and osteoporosis was treated with flucloxacillin 12 g/day for a spondylodiscitis due to *S. aureus*. She had been taking acetaminophen 3 g/day for two months. After three weeks of treatment she developed shortness of breath without signs of an exacerbation of COPD. Besides a tachypnoea (respiratory rate of 30/min) the physical examination was unremarkable. Her BMI was 23 kg/m². The chest X-ray did not show any new pathology. Arterial blood gas analysis revealed a metabolic acidosis: pH 7.29, pCO_2 23 mmHg (3.1 kPa), bicarbonate 10.9 mmol/l, base excess -15.7, pO_2 81 mmHg (10.8 kPa). The normal serum lactate of 1.6 mmol/l could not explain the whole anion gap of 29 mEq/l. She had a serum creatinine of 183 µmol/l (Cockcroft-Gault clearance of 28 ml/min). The most likely cause of the renal failure was a combination of diabetes, use of gentamycin in the past and urinary tract infections. The cholestatic liver enzymes were elevated (ALP 391 U/l, γGT 523 u/l). Before the diagnosis of spondylodiscitis was made, she had been ill for quite a while and suffered from a severe bleed from a duodenal ulcer. Tube feeding was initiated but the patient repeatedly removed the nasogastric tube. Because of the possibility of 5-oxoproline as a cause of high anion gap metabolic acidosis, flucloxacillin and acetaminophen were stopped and she was treated with bicarbonate (8.4%) and acetylcysteine (600 mg/8 hours) infusion. The patient and her husband did not want her to be transported to the ICU and unfortunately she died of respiratory insufficiency. Autopsy was not permitted. In the plasma a very high 5-oxoproline was demonstrated.

Table 1. *Laboratory results*

	Patient 1	Patient 2	Patient 3
pH	**7.12**	**7.20**	**7.29**
$HCO3^-$ (22-26 mmol/l)	**3.5**	**10**	**10.9**
Anion gap (8-16 mEq/l)	**24.5**	**26**	**24.1**
Anion gap corrected for albumin (mEq/l)	**31.75**	**28.25**	**29.1**
Lactate (< 2.2 mmol/l)	0.7	1.3	1.6
Albumin (35-52 g/l)	**15**	**31**	**20**
Creatinine (60-110 µmol/l)	**241**	155	189
Creatinine clearance CG (125-135 ml/min)	**20**	**27**	**28**
Na^+ (136-146 mmol/l)	143	141	142
K (3.6-4.8 mmol/l)	3.7	**3.4**	3.6
PO_4^{3-} (0.7-1.4 mmol/l)	**2.21**	1.11	1.2
Ca^{2+} (2.2-2.6 mmol/l)	2.1	2.15	1.9
Cl^- (98-108 mmol/l)	**115**	105	107
C-reactive protein (<8 mg/l)	**76**	**12**	**92**
Leucocytes (4.0-10.0 10 x 9/l)	**14.6**	8.5	9.1
Bilirubin (<20 µmol/l)	6	4	7
Alkaline phosphatase (<120 U/l)	**191**	**382**	**391**
γ-GT (<40 U/l)	**117**	**534**	**523**
ASAT (<30 u/l)	20	14	24
ALAT (<35 u/l)	74	15	**41**
Prothrombin time (0.8-1.2 INR)	**1.65**	1.05	1.10
TSH (0.3-4.5 mu/l)	3.1	3.9	4.1
Plasma oxoproline (≤15 µmol/l)	**6573**	**2292**	**1050**
Urinary oxoproline (<100 µmol/mmol creat)	**16,623**	**4184**	-

CG = Cockcroft-Gault; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; TSH = thyroid stimulating hormone; INR = international normalised ratio. Bold indicates abnormal values.

DISCUSSION

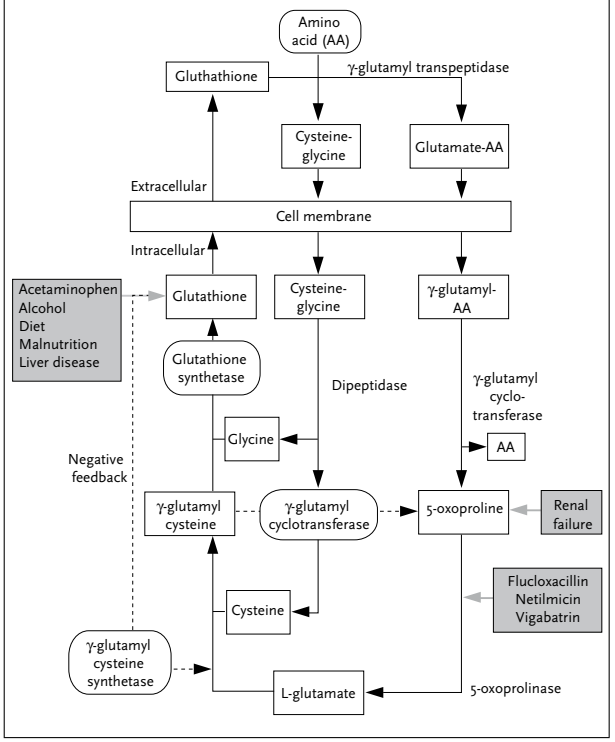
Pyroglutamic acidaemia is a rare cause of high anion gap metabolic acidosis.

Calculation of the anion gap might be helpful in the differential diagnosis of metabolic acidosis. The anion gap is the difference between the plasma concentration of the major cations (Na^+) and the major measured anions (Cl^- and HCO_3^-) and is the difference between the unmeasured anions and the unmeasured cations.[1] In our patients the anion gap was markedly elevated (normal between 8 and 16 mEq/l). A fall in cations might cause just a small rise in anion gap, so the cause should be found in elevated unmeasured anions. The normal value for the anion gap must be adjusted downwards in patients with hypoalbuminaemia (2.5 mEq/l for every 10 g/l decline in the plasma albumin concentration).[1] In all three cases the lactate was either normal or slightly elevated. No ketones could be demonstrated in the urine. Ingestion of, for example, ethylene glycol, methanol and salicylate was very unlikely in the two patients in the

hospital and could be excluded in the other patient because of the normal osmolal gap. A normal creatinine kinase in all three patients excluded rhabdomyolysis as a cause. The renal function in all patients was diminished but could not explain the whole anion gap. Acidosis in renal failure is principally due to an accumulation of acids and a reduction in ammonium production due to decreased nephron mass. Acute renal failure typically presents with a combination of hyperchloraemic acidosis and high anion gap metabolic acidosis. Bicarbonate levels usually remain >15 mmol/l, and the anion gap does not usually exceed 20 mEq/l. In all three cases we demonstrated very high levels of 5-oxoproline which caused the acidosis. The fact that the levels of oxoproline in the three cases differ more than the level of the anion gap might be explained by the fact that measurements were not taken at the same moment in all cases and the anion gap might have been higher than our measurements indicated.

In the γ-glutamyl cycle the main tripeptide glutathione (glutamic acid, cysteine and glycine) plays an important role in immunomodulation, amino acid transport and detoxification. The enzymes glutathione synthetase and γ-glutamyl cysteine synthetase produce glutathione. A negative feedback of glutathione on γ-glutamyl cysteine synthetase regulates the activity of this enzyme.[2] Depletion of glutathione activates the enzyme in producing γ-glutamyl cysteine out of cysteine and glutamate. Gamma-glutamyl cysteine can be converted to glutathione by glutathione synthetase. With a high level of γ-glutamyl cysteine, γ-glutamyl cyclotransferase converts it directly to 5-oxoproline.[3] 5-Oxoproline is oxidised to glutamate by 5-oxoprolinase. This is a rate-limiting step and with a high level of 5-oxoproline, accumulation of 5-oxoproline occurs in the blood which causes acidosis.[4] Glutathione is found in all cells but mainly in the liver. Depletion of glutathione might be caused by acetaminophen,[5,6] diets,[7] severe sepsis, chronic alcohol abuse and diminished liver function. Renal failure causes diminished clearance of 5-oxoproline.[8] Some drugs such as flucloxacillin, vigabatrin, and netilmicin might inhibit the oxidation of 5-oxoproline.[7] Almost all case reports in the literature about transient 5-oxoproline concern women,[9] probably due to the difference in activity of certain enzymes between men and women. Besides the known inherited causes of high 5-oxoproline (glutathione synthetase and 5-oxoprolinase deficiency), the cause of transient 5-oxoprolinaemia is multifactorial.[4] It is unknown whether the symptoms are fully explained by acidosis. Oxoproline might cause symptoms as well. Treatment consists of withdrawing the causes and bicarbonate infusion might be considered in a severe acidosis (e.g. pH <7.0). Acetylcysteine might restore glutathione levels by cysteine.[8,10] In an unexplained metabolic acidosis it is worth calculating the anion gap. In a patient with the above-mentioned risk factors and an unexplained high anion gap metabolic acidosis, the possibility of 5-oxoproline as a cause should always be considered. It is easy to treat and might prevent unnecessary diagnostic tests and mortality. If clinicians do not consider the possibility of 5-oxoproline as a cause of a high anion gap metabolic acidosis, the real incidence of this condition will never be known.

Figure 1. *Gamma-glutamyl cycle*



CONCLUSION

Our advice to clinicians is to consider the possibility of 5-oxoproline induced metabolic acidosis in patients with an unexplained high anion gap and the above-mentioned conditions, such as renal insufficiency, malnutrition in combination with the use of the above-mentioned drugs.

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