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High anion gap metabolic acidosis: use the proper acronym, discard the red herrings and thou shall find the culprit

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Case

A 77-year-old male, with stable chronic kidney disease stage 3, type 2 diabetes and peripheral vasculopathy, was admitted to our hospital for treatment of a badly healing diabetic ulcer on the right hallux. Empirical therapy with intravenous flucloxacillin was started. A wound swab subsequently showed growth of methicillin sensitive *Staphylococcus aureus*. His maintenance therapy, consisting of metformin, low dose aspirin and candesartan, was continued. Delayed healing prompted a vascular work-up, followed by percutaneous transluminal angioplasty of the right external iliac artery. Despite these interventions, the ulcer deteriorated and 2 weeks later the right hallux had to be amputated. During the ensuing 2 weeks, the surgical wound healed reasonably well, but the patient's general condition degraded with progressive nausea and anorexia. Physical examination revealed discrete abdominal tenderness and diminished bowel sounds. Biochemistry showed no major inflammation, but serum creatinine had risen from a baseline value of 1.3–2.0 mg/dL, which led to the cessation of metformin and candesartan. His glycaemia remained well controlled. During the next 24 h, he became hypotensive (70/30 mmHg) and started to hyperventilate vigorously. He was started on intravenous (IV) fluids and was transferred to the intensive care unit (ICU). Results of blood samples taken upon admission to the ICU, and additional blood and urine tests, obtained 12 h later, are summarized in Table 1. An abdominal computed tomography-angioscan was performed with iso-osmolar contrast after intravenous administration of isotonic $NaHCO_3$ and allowed to rule out intestinal ischaemia. His blood pressure ameliorated slightly and diuresis remained well preserved.

Question

What is causing the high anion gap metabolic acidosis in this patient?

Discussion

The relatively low levels of lactic acid led us to reconsider some of the other anions from the well-known acronym 'KUSSMALE'. However, all could be swiftly discarded by retrospective (hetero) anamnesis with some doubt left for the K&U. Indeed, although the dipstick was negative, it only reliably detects acetone and aceto-acetate. However, β-hydroxy butyric acid is a ketone typically found in combination with alcohol abuse and starvation—which did not fit our patient's state exactly except for some degree of chronic malnutrition. Although his serum creatinine had significantly risen, the corresponding estimated glomerular filtration rate was still above the levels at which uraemic acidosis develops and oliguria did not develop. The high urinary anion and osmolal gap obtained after administration of IV fluids were suggestive of urinary excretion of an organic anion with an adequate increase in renal NH_4^+ production. Could it still be lactic acid? D-lactate is not measured by most lactate assays and is abundantly excreted in the urine. However, our patient's clinical history did not correlate with the usual presentation of a patient with short bowel, showing signs of inebriation without alcoholaemia after consumption of carbohydrates.

A web search gave the final hint to the solution in the form of alternative acronyms for high anion gap acidoses, such as MUDPILES, CUTE DIMPLES and GOLDMARKS [1]. It was the 'O' for 5-oxoproline in the latter acronym that drew our attention to the medical prescription file of the patient. Although he had only occasionally received acetaminophen (never exceeding 2 g daily) for pain relief during the first 2 weeks of the hospital admission, high doses of flucloxacillin had been administered for 6 weeks, resulting in a cumulative dose of ∼500 g! Subsequent measurement of 5-oxoproline in the urine revealed a concentration of 11 869 mmol/mol creatinine (normal value <100). A few days after cessation of the antibiotic, he recovered completely.

High anion gap metabolic acidosis through accumulation of 5-oxoproline has been described since 1989. It is caused by a disruption of the γ-glutamyl cycle (Figure 1), which is related to the synthesis of the ubiquitous antioxidant glutathione and uses this tripeptide for intracellular transport of amino acids. In most cases the underlying mechanism is a combination of glutathione deficiency induced by chronic acetaminophen treatment and cysteine and/or glycine deficiency. This is further enhanced by relative ATP depletion associated with chronic illness and

probably diabetes. Women are especially susceptible to this mechanism with 40/49 of all reported cases being female. This phenomenon could be explained by gender-specific differences in glutathione stores and acetaminophen metabolism [2]. The presented case does not perfectly fit with this description and resembles better the smaller fraction of cases reported with flucloxacillin, netilmicin and vigabatrin. Whereas vigabatrin is metabolized directly to oxoproline, flucloxacillin and netilmicin have an inhibitory effect on the oxidation of 5-oxoproline by 5-oxoprolinase [3, 4]. However, virtually all those reports mention concurrent triggers such as malnutrition and use of acetaminophen to some extent, as was the case in our patient [2, 5].

Table 1. Laboratory measurements

Laboratory measurements upon admission to ICU		
Arterial	Venous	Urine
pH 7.15	[Na+] 142 mmol/L	Ketones negative
$PaCO_2$ 8 mmHg	[K+] 3.3 mmol/L	Glucose negative
PaO_2 120 mmHg	$[Cl^-]$ 100 mmol/L	
Lactic acid 5.8 mmol/L	$[HCO_3^-]$ 5 mmol/L	
Laboratory measurements 12 h after admission to ICU		
	Blood	Urine
pH	7.36	6.0
[Na+]	140 mmol/L	39 mmol/L
[K+]	3.3 mmol/L	76 mmol/L
$[Cl^-]$	100 mmol/L	17 mmol/L
[Creatinine]	2.00 mg/dL	
[Ureum]	39 mg/dL	58 mg/dL
$[HCO_3^-]$	7 mmol/L	
Osmolality	304 mosmol/kg	427 mosmol/kg

Inborn errors of metabolism have also been described in association with excessive oxoprolinaemia: oxoprolinase deficiency is inherited as an autosomal recessive trait and generates a dramatic phenotype with neonatal hypoglycaemia and mental retardation. It is extremely rare: only eight cases have been described. Glutathione synthetase deficits have been observed more frequently and have a more variable phenotype ranging from major neurological manifestations to enhanced susceptibility to intravascular haemolysis. At least 10 different underlying point mutations in the encoding gene have been elucidated at present. Liss *et al.* suggest that a heterozygous state for these mutations might explain why patients accumulate 5-oxoproline to a clinically relevant extent in the context of severe stress on the γ-glutamyl cycle [5].

Acetylcysteine, a therapeutic cornerstone in the treatment of acute acetaminophen toxicity, is considered to be beneficial by repleting glutathione as a cysteine donor. Its empirical use has been reported in several case reports. However, it could theoretically increase γ-glutamylcysteine up to levels which might saturate glutathione synthetase with subsequent overflow to metabolism by γ-glutamylcyclotransferase and hence paradoxical increases of 5-oxoproline [5].

We conclude that this patient had a metabolic high anion gap acidosis through accumulation of 5-oxoproline. Major cause was the administration of high-dose flucloxacillin over a long period of time. Contributing factors were diabetes, malnutrition and the occasional intake of acetaminophen. As recent advances in pathophysiology and genetics seem to identify a potential reservoir of vulnerable patients, it is possible that this condition might be overlooked more often than is commonly assumed. By consequence, it is recommended that high anion gap acidosis in patients without 'classical' anions triggers an evaluation for 5-oxoproline.

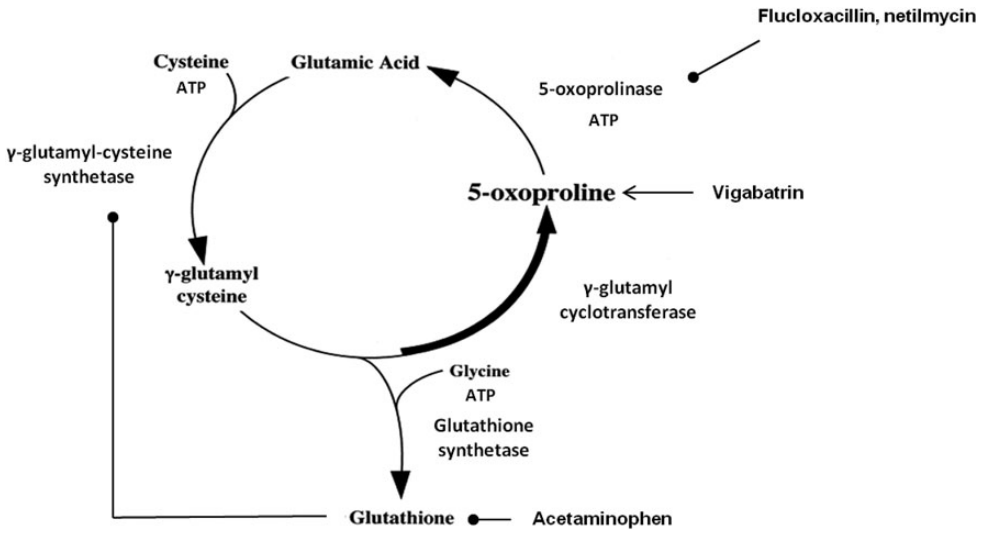

Fig. 1. The γ-glutamyl cycle—a schematic overview. Gluthatione is a tripeptide synthesized from glutamic acid, cysteine and glycine with the consumption of 2 ATP. It has a negative feedback on its own production by inhibition of γ-glutamyl-cysteine synthetase. When glutathione stores are depleted, either by acetaminophen, low energy states or relative glycine/cysteine deficiency, this negative feedback loop is annihilated, resulting in accumulation of γ-glutamyl-cysteine. In turn this metabolite is transformed to 5-oxoproline by γ-glutamylcyclotransferase. 5-Oxoproline is normally recycled to glutamic acid by 5-oxoprolinase with the consumption of 1 ATP. 5-Oxoprolinase is inhibited by low energy states, flucloxacillin and netilmicin. Vigabatrin is metabolized to 5-oxoproline. Dots indicate inhibition.

Conflict of interest statement. None declared.

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