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CASE REPORT Open Access

A case report of Paracetamol related pyroglutamic acidosis: mind the gap in a malnourished patient

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Abstract

Background Pyroglutamic acidosis is a rare cause of high anion gap metabolic acidosis. Most cases of paracetamol related pyroglutamic acidosis are described in malnourished women and patients with kidney/liver failure, alcohol use or severe sepsis. In this report, we describe how pyroglutamic acidosis could be related to the use of chronic therapeutic paracetamol with only malnutrition as an associated risk factor.

Case presentation We report a case of a 67-year-old male patient developing a pyroglutamic acidosis. The patient was initially admitted to hospital for infectious osteoarthritis and developed a metabolic acidosis during his hospital stay. Analgesics included daily therapeutic doses of paracetamol. What makes our case unusual is that our malnourished male patient did not have renal or hepatic failure. The diagnosis of paracetamol related pyroglutamic acidosis was made after ruling out the main causes of metabolic acidosis. It was further confirmed by urine organic acids measurement showing a markedly elevated level of pyroglutamic aciduria. Paracetamol was discontinued allowing a prompt correction of the anion gap.

Conclusion This case is a representative of pyroglutamic acidosis related to chronic therapeutic paracetamol with only malnutrition as an associated risk factor. Physicians should be aware of such unusual cause of metabolic acidosis, which may be more common than expected in hospitalized patients. A high clinical suspicion is needed when urine organic acids analysis is not available.

Keywords High anion gap metabolic acidosis, Malnutrition, Paracetamol, Pyroglutamic acidosis, Case report

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Background

Pyroglutamic acidosis is due to the accumulation of pyroglutamic acid (5-oxoproline). It is a rare but likely underdiagnosed cause of high anion gap metabolic acidosis (HAGMA), which can be acquired due to the chronic use of paracetamol at therapeutic doses. This typically occurs in women, in the setting of malnutrition, severe sepsis, chronic alcohol use, liver or kidney failure. Use of other drugs, such as vigabatrin, netilmicin and flucloxacillin, was also reported as an alternative cause of pyroglutamic acidosis. [1, 2]

Here, we report a case of pyroglutamic acidosis related to therapeutic paracetamol use in a malnourished male patient.

Case presentation

A 67-year-old male patient was admitted to hospital for infectious osteoarthritis of the femoral head. He had a past medical history of hypertension, type 1 diabetes mellitus and controlled Human Immunodeficiency Virus infection. The joint was initially debrided, and the osteoarthritis was controlled by prolonged antibiotherapy including Imipenem 1 g three times daily and Fluconazole 400 mg once daily. The treatment also included short acting insulin, Odefsey (Emtricitabine, Rilpivirine, Tenofovir alafenamide) 200/25/25 once daily, Arunavir 800 mg twice daily, Ritonavir 100 mg twice daily, Tivicay (Dolutegravir) 50 mg twice daily, Aspirin 75 mg daily. Analgesics included Paracetamol 1–2 g daily, Actiskenan (Morphine sulfate) 10 mg daily and Nefopam 20 mg, as needed.

A profound metabolic acidosis developed at 6-months of his hospital stay. Our patient had poor food intake and low tolerance of oral dietary supplements in the past two weeks. He also suffered from generalized weakness but no obvious neurological deficit on examination. The blood pressure was well controlled. He denied any alcohol or alternative drug use. Laboratory data at the day of diagnosis showed serum bicarbonate level 13mmol/L, anion gap 22mEq/L, creatinine 0.72 mg/dL, albumin 2.7 g/dL. An arterial blood gas revealed a pH of 7.40, PaCO2 25mmHg, Bicarbonate 13mmol/L and PaO2 100mmHg. The serum lactate level was 1.2mmol/L. The serum salicylate, B-hydroxybutyrate and alcohol levels were normal. (Table 1)

The patient displayed a high-anion gap metabolic acidosis (HAGMA): serum anion gap (AG), corrected for hypoalbuminemia equalled 25.3, c AG = AG + 2.5 (4-albumine in g/dL). This HAGMA has an appropriate respiratory response. We compared the increase in serum anion gap and the bicarbonate deficit using the delta ratio that indicated an absence of concurrent metabolic acidosis due to the loss of bicarbonate. The most common causes of HAGMA are listed in the mnemonic "GOLDMARK": Glycol, Oxoproline, L lactate, D lactate, Methanol, Aspirin, Renal failure and Ketoacidosis. [3] Our patient had a controlled infection and no evidence of hypovolemia or hemodynamic instability along with a normal serum lactate level. Alternative causes of HAGMA due to ketoacidosis or salicylate abuse were ruled out. HAGMA in our case does not generate an osmolal gap: the measured osmolality was only 10 mOsmol/Kg greater than his calculated osmolality (normal value ≤ 10) making the ingestion of alcohol or glycol unlikely. The possibility of pyroglutamic acidosis due to the chronic use of paracetamol was suspected (1–2 g daily for 6 months). Paracetamol was withheld and alternative medications for pain management were prescribed. Serum amino acid levels were checked and showed a generalized hypoaminoacidemia consistent with the malnourished status of our patient. (Table 1)

Table 1 Laboratory data at diagnosis

	Patient's values	Normal range
Venous blood		
Sodium, mmol/L	142	135-145
Potassium, mmol/L	3.6	3.5-5.0
Bicarbonate, mmol/L	13	22-26
Chloride, mmol/L	107	98-110
Albumin, g/dL	2.7	3.5-5.0
Glucose, mg/dL	86	70-110
Urea, mg/dL	18	6-20
Creatinine, mg/dL	0.72	0.5-1.5
Anion gap	22	12
Measured Osmolality, mOsm/Kg	305	278-298
Calculated Osmolality, mOsm/kg	295	270-290
Alcohol level	Negative	Negative
Arterial blood gas		
pH	7.40	7.35-7.45
PaCO2, mmHg	25	35-45
Bicarbonate, mmol/L	13	22-26
PaO2, mmHg	100	80-105
Serum amino acids (µmol/L)*:		
Arginine	30	40-124
Valine	145	178-318
Cystine	25	43-131
Methionine	11	14-42
Leucine	70	87-175
Tyrosine	33	37-89

**Only serum amino acids with low levels are shown in this table*

Pa CO_2 arterial partial pressure of carbon dioxide; Pa O_2 arterial partial pressure of oxygen

The diagnosis was further confirmed by urine organic acids measurement, showing a markedly elevated level of pyroglutamic aciduria (932 µmol per mmol of creatininuria, normal < 18 µmol/mmol).

Discussion and conclusion

Pyroglutamic acidosis is due to the accumulation of pyroglutamic acid (or 5-oxoproline), an endogenous organic acid and an intermediate in the γ-glutamyl cycle, a pathway of glutathione metabolism (Fig. 1A). [4] Chronic

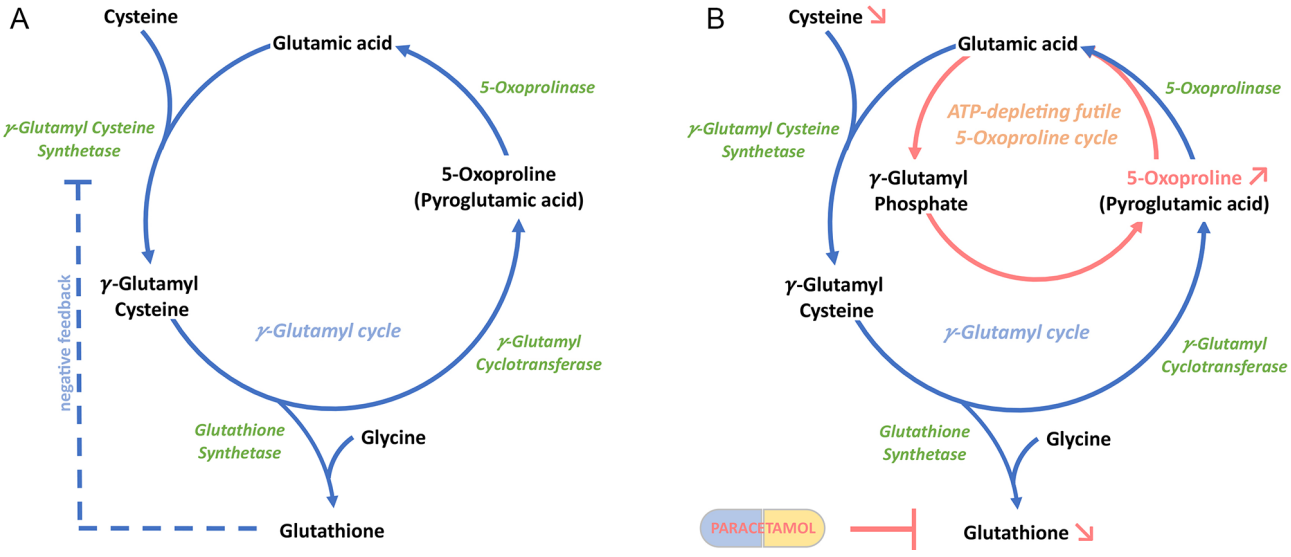

Fig. 1 (**A**) The γ-glutamyl cycle. (**B**) The ATP depleting 5-oxoproline cycle the effect of paracetamol on γ-glutamyl cycle leads to an ATP depleting futile 5-oxoproline cycle resulting in pyroglutamic acidosis

ingestion of paracetamol consumes glutathione stocks as well as cysteine and other sulfated amino acids. The decrease in intracellular glutathione level removes the negative feedback on γ-glutamyl cysteine synthetase and increases the production of γ-glutamyl cysteine. A dietary deficit in glycine slows the production of glutathione, hence γ-glutamyl cysteine is converted into 5-oxoproline. When cysteine is deficient due to malnutrition, the γ-glutamyl cysteine cannot be produced, and glutamic acid is rather transformed into γ-glutamyl phosphate, which in turn will autocyclize to form the 5-oxoproline. The 5-oxoprolinase may regenerate glutamate from 5-oxoproline, but in an ATP-depleting futile cycle that eventually results in a progressive depletion of ATP and further accumulation of 5-oxoproline (Fig. 1B). [5]

An empirical diagnosis of pyroglutamic acidosis can be made when the urine organic acid measurement is not readily available. N-acetyl cysteine may be beneficial to accelerate the resolution of acidosis as described by Green et al. and Reed et al. who reported pyroglutamic acidosis in malnourished patients presenting with confusion. [6, 7] In our case, there was no neurological symptoms. The metabolic acidosis corrected over 10 days after the withdrawal of paracetamol without further treatment. Early discontinuation of the causative drug alongside a dietary consultation improved the general status of our patient. Repeated urine organic acid analysis two weeks later showed normal levels of pyroglutamate.

In conclusion, pyroglutamic acidosis related to chronic therapeutic paracetamol should be suspected in malnourished patients. An early diagnosis should lead to the prompt discontinuation of paracetamol.

Abbreviations

HAGMA High-anion gap metabolic acidosis
AG Anion gap

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R.E. analyzed and interpreted the patient data and was a major contributor in writing the manuscript. M.Z. supervised and contributed in writing the manuscript. All authors interpreted the data, read and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

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