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Case Report

A not so simple analgesic

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Abstract

Many of the common causes of a high anion gap metabolic acidosis, like salicylate toxicity or diabetic ketoacidosis, are well recognized and promptly treated. Pyroglutamic acidosis (or 5-oxoproline acidosis) is a less common cause and is likely substantially underdiagnosed for two reasons: firstly, urine or serum measurements of pyroglutamic acid are performed only in specialist laboratories, and secondly, because awareness of the condition is still low, despite widespread reports in the medical and biochemical literature. The condition is often precipitated by the chronic use of paracetamol. Paracetamol is increasingly being widely prescribed as an alternative to NSAIDs often in maximal doses, given its innocuous reputation, and we anticipate more similar presentations. We present a case of a young pregnant woman who developed a severe metabolic acidosis secondary to raised pyroglutamate. Her treatment necessitated an emergency Caesarean section, ventilation and haemodiafiltration, despite normal renal function. We provide a reminder of other risk factors associated with the diagnosis.

Keywords: acidosis; anion gap; oxoproline; paracetamol; pyroglutamate

Presentation

A 21-year-old pregnant woman presented at full term with her second pregnancy to Accident and Emergency with a 2-week history of shortness of breath and eating poorly. Other symptoms included intermittent frontal headaches with vomiting, and back and rib pain. There had been no complications with her first pregnancy. She had been taking regular paracetamol and co-codamol over the previous year for tempero-mandibular joint pain. She had no significant family history. She was a smoker of 15/day but denied recent alcohol or illicit drug use. She was not on any other prescribed medication other than varying doses of paracetamol at ~3 g/day. She had been seen twice in the previous week, and been prescribed a course of amoxicillin for a presumed UTI, followed by erythromycin for a chest infection. She was given further amoxicillin in A & E for a chest infection and transferred to the labour ward.

Over the next few hours, her respiratory rate increased from 22 to 26 per minute; on examination, there was a mild expiratory wheeze. Arterial blood gas sampling was taken on air. This showed a severe metabolic acidosis: pH 7.26, pCO_2 1.27 kPa, pO_2 16.4 kPa, base deficit 22.5 mEq/L and HCO_3 4.2 mmol/L.

Furthermore, blood results showed: creatinine 79 μmol/L, normal lactate 1.6 mmol/L, low glucose 2.7 mmol/L, sodium 134 mmol/L, bicarbonate <5 mmol/L, chloride 104 mmol/L and albumin 39 g/L. The anion gap was calculated as >25 mEq/L, and the serum osmolality was normal, with no significant osmolal gap. There was only one plus ketonuria demonstrated on dipstick urinalysis. No salicylate was detectable, and paracetamol levels were 14 mg/L, consistent with recent use of the drug. Other abnormalities included a raised white cell count (17.2×10^9/L, neutrophilia) and raised MCV (101.9 fL), despite recently normal folate and B12 determinations, and a blood film showed mild macrocytosis and anisocytosis. The alkaline phosphatase was 339 u/L (42–128), and γ-GT 202 u/L (6–42). The chest radiograph was normal.

During this period of assessment, the patient developed uterine contractions, and CTG recordings detected prolonged decelerations 30 min later. The baby was delivered by Caesarean section under general anaesthetic. A live male was delivered in initially poor condition and transferred to SCBU. His mother was taken to intensive care for haemofiltration and ventilation, which were continued for 24 h. She was treated with antibiotics, transfused and given high potency vitamin B. Further paracetamol was advised against. *Haemophilus influenzae* was isolated from a tracheal suction sample. She was able to go home with her baby 6 days after her initial presentation.

As no other cause for the severe metabolic acidosis had been identified, urine at presentation to ITU was sent for organic acid testing. This revealed a markedly raised pyroglutamate to creatinine ratio at 4.97 (normal <0.1) (Figure 1). Other urinary organic acids/creatinine ratios showed only moderate elevation: pyruvate (0.18), 3-hydroxybutyrate (0.15), lactate (0.15), 2-hydroxybutyrate and 2-oxo-isocaproate (neither quantified but 'very mildly elevated'). Convalescent serum and urine showed no amino acid, or other organic acid or carnitine disorder, and a now normal urine pyroglutamate level.

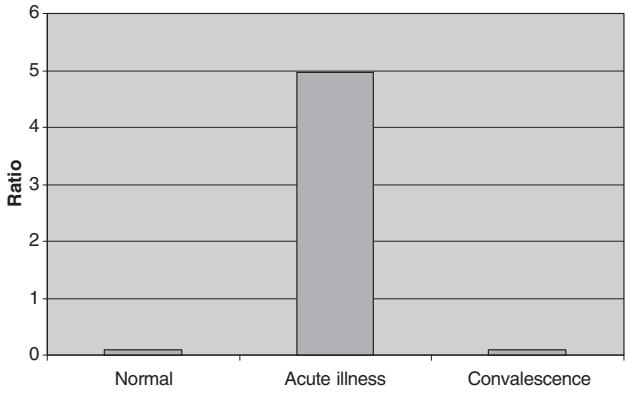

Fig. 1. Urine pyroglutamate to creatinine ratio.

Table 1. Risk factors for pyroglutamic acidosis

Chronic therapeutic paracetamol ingestion [1,2]
Alcohol abuse [3]
Liver disease [1]
Malnutrition [4,5]
Pregnancy [6,7]
Renal insufficiency [8]
Female sex [9]
Flucoxacillin, vigabatrin and netilmicin [9,10]

Discussion

Pyroglutamic acid (5-oxoproline) is an intermediate in the γ-glutamyl cycle. This cycle comprises a series of enzymic reactions responsible for the synthesis and utilization of glutathione. Glutathione is a critically important tripeptide, comprised of cysteine, glycine and glutamic acid. It has major reducing and anti-oxidant effects and plays a central role in detoxification; the liver is its primary storage site. Inherited defects of the γ-glutamyl cycle, for example glutathione synthase deficiency, are rare, and patients present at an early age with neurological and haematological manifestations.

There are an increasing number of reports of acquired pyroglutamic acidosis in patients with no evidence of any inherited defect of the γ-glutamyl cycle. Table 1 lists some reported clinical associations, and our patient demonstrated five of these. A factor linking most of these is a relative glutathione deficiency. The mechanism for this is outlined in Figure 2. Glutathione deficiency results in a loss of negative feedback inhibition of γ-glutamyl cysteine synthase. The absence of glycine or reduced activity of glutathione synthase leads to an accumulation of γ-glutamyl cysteine and its conversion to pyroglutamic acid through an alternative pathway catalysed by γ-glutamyl cysteine cyclotransferase. The conversion of pyroglutamic acid to glutamic acid is catalysed by a rate-limiting step, and so, pyroglutamic acid accumulates. Other contributors are reduced renal clearance of pyroglutamic acid and glycine deficiency, and flucloxacillin is thought to inhibit 5-oxoprolinase.

Our patient had been eating poorly throughout her pregnancy but denied alcohol use. The antibiotics prescribed for her presumed UTI were not recognized to cause pyroglutamic acidosis, but she had been taking prolonged high-dose paracetamol. This factor is important to recognize since immediate cessation is indicated, and there may be a role for *N*-acetyl-cysteine. We advocate greater vigilance for high anion gap metabolic acidosis with pro-

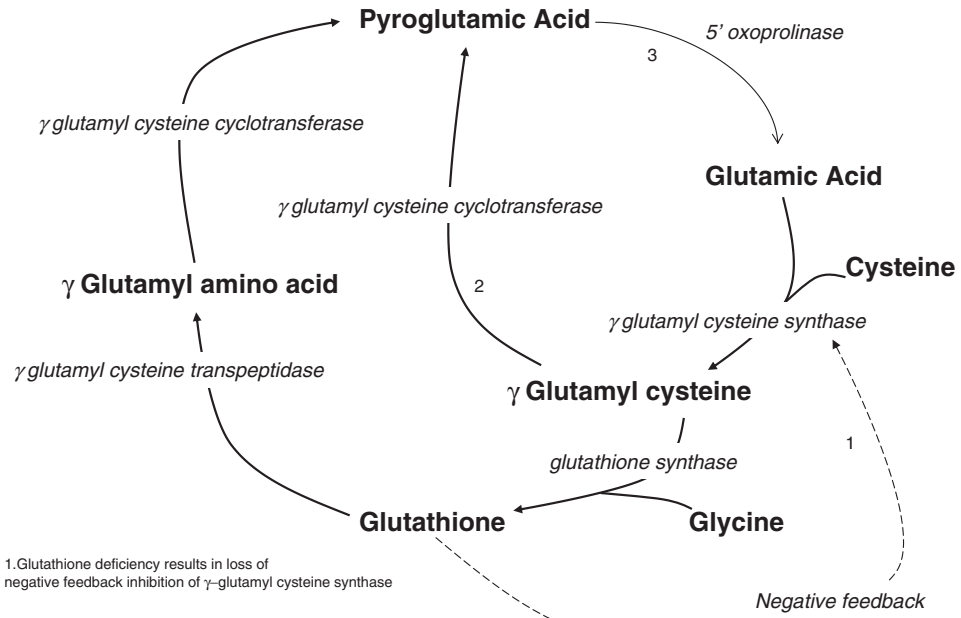

Fig. 2. γ-Glutamyl cycle.

longed courses of high-strength paracetamol in these groups of patients.

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Conflict of interest statement. None declared.

References

1. Fenves AZ, Kirkpatrick HM III, Viralkumar VP *et al*. Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. *Clin J Am Soc Nephrol* 2006; 1: 441–447
2. Pitt JJ, Hauser S. Transient 5-oxoprolinuria and high anion gap metabolic acidosis: clinical and biochemical findings in eleven subjects. *Clin Chem* 1998; 44: 1497–1503
3. Ookhtens M, Kaplowitz N. Role of the liver in interorgan homeostasis of glutathione and cyst(e)ine. *Semin Liver Dis* 1998; 18: 313–329
4. Persaud C, Forrester T, Jackson AA. Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. *J Nutr* 1996; 126: 2823–2830
5. Jackson AA, Badaloo AV, Forrester T *et al*. Urinary excretion of 5-oxoproline (pyroglutamic acid) as an index of glycine insufficiency in normal man. *Br J Nutr* 1987; 58: 207–214
6. Jackson AA, Persaud C, Werkmeister G *et al*. Comparison of urinary 5-L-oxoproline (L-pyroglutamate) during normal pregnancy in women in England and Jamaica. *Br J Nutr* 1997; 77: 183–196
7. Persaud C, McDermott J, De Benoist B *et al*. The excretion of 5-oxoproline in urine, as an index of glycine status, during normal pregnancy. *Br J Obstet Gynaecol* 1989; 96: 440–444
8. Humphreys BD, Forman JP, Zandi-Nejad K *et al*. Acetaminophen-induced anion gap metabolic acidosis and 5-oxoprolinuria (pyroglutamic aciduria) acquired in hospital. *Am J Kidney Dis* 2005; 46: 143–146
9. Kortman W, van Agtmael MA, van Diessen J *et al*. 5-Oxoproline as a cause of high anion gap metabolic acidosis: an uncommon cause with common risk factors. *Neth J Med* 2008; 66: 354–357
10. Croal BL, Glen AC, Kelly CJ *et al*. Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult patient receiving antibiotic therapy. *Clin Chem* 1998; 44: 336–340

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