# Pyroglutamic Acidosis: A Rare and Underdiagnosed Cause of High Anion Gap Metabolic Acidosis

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## Introduction:

High anion gap metabolic acidosis (HAGMA) is a common metabolic disorder encountered in the ICU setting. A likely underdiagnosed cause of HAGMA is pyroglutamic acidosis (5-oxoprolinuria), a condition caused by a defect in the gamma-glutamyl cycle. Initially recognized as the result of a hereditary enzyme deficiency leading to significant metabolic abnormalities early in life, an increasing number of pyroglutamic acidosis cases have been reported in previously unaffected adults due to an acquired defect in the gamma-glutamyl cycle, nearly all associated with acetaminophen use. We present the case of a patient who developed severe pyroglutamic acidosis while on chronic acetaminophen therapy.

## Case Presentation:

***History:*** A 58-year-old Caucasian female presented to the emergency department complaining of a three-day history of rapidly progressive dyspnea. Review of systems was positive for poor oral intake, headache, dyspnea, chest tightness, and two episodes of vomiting. Past medical history included hypertension, peptic ulcer disease, chronic low back pain, depression, and anxiety. She denied any known history of renal disease. Medications included omeprazole, duloxetine, aripiprazole, lorazepam, amitriptyline, melatonin, hydrocodone/acetaminophen and acetaminophen. She noted that she had been recently taking a significantly increased amount of acetaminophen for pain. The patient cited a 40 pack-year smoking history and quit ten years ago. She denied ingestion of ethanol, methanol, paraldehyde, ethylene glycol, or any illicit substances.

***Physical Exam:*** Vital signs on admission were as follows: 97.4°F, blood pressure 142/72, pulse 143, respirations 28, and oxygen saturation 99% on room air. Physical examination simply revealed a well-nourished but acutely ill-appearing female in mild respiratory distress.

***Diagnostic Data:*** Initial laboratory studies (Table 1) revealed a high anion gap metabolic acidosis with pH 7.02, HCO3 9, and anion gap 21. Workup was negative for elevated lactate or salicylate levels, ketoacidosis, uremia, or evidence of methanol or ethylene glycol poisoning. The urine organic acid screen revealed a markedly elevated level of pyroglutamic acid.

***Clinical Course:*** Based on the patient's laboratory studies and clinical findings, she was diagnosed with pyroglutamic acidosis associated with acetaminophen ingestion. Her acidosis resolved with discontinuation of all acetaminophen-containing compounds, volume resuscitation, and administration of intravenous sodium bicarbonate. The patient rapidly improved with treatment and was discharged home in stable condition on the fourth day of hospitalization with instructions to discontinue acetaminophen use indefinitely.

## Discussion:

***Pathogenesis:*** Pyroglutamic acidosis occurs as a result of a defect in the gamma-glutamyl cycle. This cycle is composed of a series of enzymatic reactions that ultimately leads to the production of the tripeptide glutathione, which serves an important role in many cells of the body- scavenging free oxygen radicals, drug detoxification, and amino acid transport (Figure 1). When normal or high levels of glutathione are present, the production of its precursor molecules is inhibited by negative feedback on the enzyme gamma-glutamylcysteine synthetase. With chronic acetaminophen use, however, glutathione stores can be depleted, leading to up-regulation of gamma-glutamylcysteine synthetase and increased production of gamma-glutamylcysteine. This molecule is normally then converted to glutathione by glutathione synthetase. However, with significant elevation in gamma-glutamylcysteine levels, conversion to glutathione becomes the rate-limiting step[1] and some gamma-glutamylcysteine enters the secondary metabolic pathway to be converted to 5-oxoproline (pyroglutamic acid)[2]. It is the build-up of this molecule that leads to severe high anion gap metabolic acidosis.

***Risk Factors:*** There are several risk factors that have been implicated in the development of pyroglutamic acidosis, particularly when combined with use of acetaminophen. These include sepsis, alcohol abuse, renal failure,[3] hepatic dysfunction, malnutrition, prematurity, pregnancy,[4] severe burns, Stevens-Johnson syndrome, urea cycle disorders, hawkinsinuria, homocysteinuria, and artificial diets.[1] Certain medications, including netilmicin, flucloxacillin, and vigabatrin, have also been linked to the disorder.[3,5] The reason for our patient's sudden development of severe metabolic acidosis after many years of being stable on chronic acetaminophen therapy was unclear but may have been precipitated by an increase in acetaminophen intake in the setting of acute malnutrition.

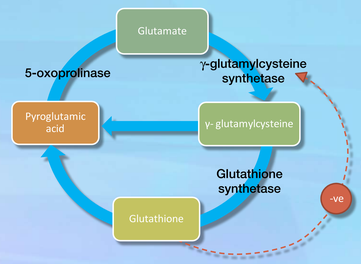
***Diagnosis:*** Diagnosis is made by recognition of high anion gap metabolic acidosis not explained by another etiology and either positive gas chromatography or detection of an elevated pyroglutamic acid level on a urine organic acid screen. Acetaminophen level may be checked in order to rule out overdose, however, a low or undetectable acetaminophen level does not rule out pyroglutamic acidosis, as most cases do occur in patients taking therapeutic doses of acetaminophen.

***Treatment:*** Initial management involves discontinuation of all acetaminophen-containing medications, reversal of severe metabolic acidosis by administration of bicarbonate-containing intravenous fluids and treatment of any co-morbid conditions. Intravenous *N*-acetylcysteine, the standard therapy for acetaminophen poisoning, may be of some benefit in the management of acquired pyroglutamic acidosis. This has not been well studied. However, with its possible therapeutic benefit in repleting glutathione stores and its low potential for toxicity, its use as an adjunctive measure does not seem unreasonable.

Table 1. **Pertinent Lab Values**

| Chemistry | | Urinalysis | |
|---|---|---|---|
| Glucose | 67 mg/dL | Specific gravity | 1.015 |
| BUN | 15 mg/dL | PH | 5 |
| Cr | 1.3 mg/dL | Protein | 100-200 mg/dL |
| $Na^+$ | 130 meq/L | Ketone | 40-60 mg/dL |
| $K^+$ | 5.8 meq/L | Glucose | negative |
| $Cl^-$ | 100 meq/L | Blood | 0.06-0.10 mg/dL |
| $HCO_3$ | 9 meq/L | Leukocyte esterase | negative |
| Anion gap | 21 | Nitrite | negative |
| $Ca^{2+}$ | 11.6 mg/dL | | |
| $P^{3-}$ | 1.4 mg/dL | **Toxicology** | |
| $Mg^{2+}$ | 2.5 mg/dL | Urine toxicology screen | negative |
| | | Aetaminophen | <10 ug/mL |
| **Arterial Blood Gas** | | Salicylates | <1 mg/dL |
| pH | 7.02 | Methanol | negative |
| $pCO_2$ | <20 mmHg | Ethanol | negative |
| $pO_2$ | 161 mmHg | Ethylene glycol | negative |
| $pHCO_3$ | <5 meq/L | | |
| Base deficit | 25.7 | **Other** | |
| $0_2$ sat, arterial | 99% | Lactate | 1.6 |
| | | Acetone | negative |
| | | B-hydroxybutyric acid | 0.89mmol/L |
| | | Serum osmolarity | 281 mosm/kg |
| | | Urine anion gap | 32 |
| | | SPEP | negative |
| | | D-lactate | negative |
| | | Pyrolutamic acid | 3767 umol/mmol or creatinine (Ref range 15-215) |

Figure 1. **The Gamma-glutamyl Cycle**




## Conclusion:

The diagnosis of pyroglutamic acidosis should be considered in the differential for any patient presenting with high anion gap metabolic acidosis, particularly if there is a history of recent acetaminophen use. Increased awareness and prompt recognition of this condition by physicians can prevent fatal outcomes and recurrences in susceptible patients.

## References:

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