CASE REPORT

Recurrent High Anion Gap Metabolic Acidosis Secondary to 5-Oxoproline (Pyroglutamic Acid)

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• **High anion gap metabolic acidosis in adults is a severe metabolic disorder for which the primary organic acid usually is apparent by clinical history and standard laboratory testing. We report a case of recurrent high anion gap metabolic acidosis in a 48-year-old man who initially presented with anorexia and malaise. Physical examination was unrevealing. Arterial pH was 6.98, Pco_2 was 5 mm Hg, and chemistry tests showed a bicarbonate level of 3 mEq/L (3 mmol/L), anion gap of 32 mEq/L (32 mmol/L), and a negative toxicology screen result, except for an acetaminophen (paracetamol) level of 7.5 μg/mL. Metabolic acidosis resolved with administration of intravenous fluids. Subsequently, he experienced 5 more episodes of high anion gap metabolic acidosis during an 8-month span. Methanol, ethylene glycol, acetone, ethanol, D-lactate, and hippuric acid screens were negative. Lactate levels were modestly elevated, and acetaminophen levels were elevated for 5 of 6 admissions. These episodes defied explanation until 3 urinary organic acid screens, obtained on separate admissions, showed striking elevations of 5-oxoproline levels. Inborn errors of metabolism in the γ-glutamyl cycle causing recurrent 5-oxoprolinuria and high anion gap metabolic acidosis are rare, but well described in children. Recently, there have been several reports of apparent acquired 5-oxoprolinuria and high anion gap metabolic acidosis in adults in association with acetaminophen use. Acetaminophen may, in susceptible individuals, disrupt regulation of the γ-glutamyl cycle and result in excessive 5-oxoproline production. Suspicion for 5-oxoproline–associated high anion gap metabolic acidosis should be entertained when the cause of high anion gap metabolic acidosis remains poorly defined, the anion gap cannot be explained reasonably by measured organic acids, and there is concomitant acetaminophen use. *Am J Kidney Dis* 46:E4-E10.**

INDEX WORDS: High anion gap metabolic acidosis; metabolic acidosis; 5-oxoprolinuria; γ-glutamyl cycle; 5-oxoproline; pyroglutamic acidosis.

HIGH ANION GAP metabolic acidosis in adults is a severe metabolic derangement that occurs in multiple clinical settings. The primary organic acid usually is ascertained by means of clinical history and a standard set of serological and urinary studies (creatinine, lactate, ketones, acetone, salicylate, methanol, and ethylene glycol levels). Less common, but still well defined, causes of high anion gap metabolic acidosis and the major associated organic acid include paraldehyde toxicity (acetic acid), D-lactic acidosis (D-lactic acid produced in the colon from fermentation of excess carbohydrates associated with short-bowel syndromes), citric acid ingestion (citric acid), and toluene ingestion (hippuric acid). Beyond these diagnoses, there have been few alternative causes of high anion gap metabolic acidosis described in adults.

Inborn errors of metabolism cause a wide spectrum of organic acidoses that usually present in infancy and childhood. Specifically, errors of metabolism in the γ-glutamyl cycle leading to recurrent 5-oxoprolinuria (pyroglutamic aciduria) are rare, but well described. Among errors of metabolism in the γ-glutamyl cycle, only glutathione synthetase deficiency is associated with high anion gap metabolic acidosis.[1] There are several recent reports of 5-oxoprolinuria and high anion gap metabolic acidosis in adults that have been attributed to transient acquired defects in the γ-glutamyl cycle.[2-9] We report the case of an adult man with 6 episodes of high anion gap metabolic acidosis during an 8-month span. His clinical presentations and measurements of a wide spectrum of organic acids defied clear identification until 3 urinary organic acid screens, obtained on separate admissions, showed pre-

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dominant and striking elevation of 5-oxoproline levels.

METHODS

Organic Acid Analysis

Organic acids were extracted by means of ethylacetate extraction of acidified urine corresponding to 0.25 mg of creatinine. After separation and evaporization of the organic phase, the residue was derivatized using *N*, *O-bis*-(trimethylsilyl) trifluoroacetamide with 1% trimethylchlorosilane. Sialyated organic acids were separated in a Hewlett-Packard 5890 gas chromatograph on an Agilent HP-5 capillary column (25 m; 0.2 mm inner diameter; film 0.33 μmol/L). A Hewlett-Packard 5989B mass spectrometer was used in electron ionization mode as detector. Excretion of 5-oxproline was determined semiquantitatively by comparison to a standard curve prepared with authentic 5-oxoproline using pentadecanoic acid as internal standard and normalized to creatinine concentration.

Glutathione Synthetase Activity

Preparation of hemolysates. Packed erythrocytes were lysed by the addition of 1 volume of 50 mmol/L of Tris-HCl buffer (pH 7.4) containing 1 mmol/L of EDTA and by sonication for 30 seconds. Erythrocyte membranes were removed by centrifugation at 18,000*g* for 40 minutes. Hemoglobin level was determined by using Vanzetti's method.[10]

Enzyme activity. Glutathione synthetase activity was determined as described[11] with the following modifications. The incubation volume of 100 μL contained 16 mmol/L of [1-14C]glycine (specific activity, 9.3 $\times$ 109 Bq/mol), 12 mmol/L of L-γ-glutamyl-L-γ-aminobutyrate, 4 mmol/L of sodium adenosine triphosphate, 4 mmol/L of phosphoenolpyruvate, 8,000 units of pyruvate kinase/l, 25 mmol/L of potassium chloride, 6 mmol/L of magnesium chloride, 1 g/L of bovine serum albumin, and 100 mmol/L of Tris-HCl (pH 8.6). The reaction was incubated for 120 minutes at 37°C and stopped by adding 10 μL of 20% perchloric acid. After removal of denatured protein by centrifugation at 17,000*g* for 2 minutes, supernatant was added to a 0.5- $\times$ 4-cm Dowex (Fluka, Buchs, Switzerland) acetate column. The remaining [1-14C]glycine was eluted with 6 mL of 20 mmol/L of acetic acid before the product (14C-γ-glutamyl-aminobutyryl-glycine, ophthalmic acid) was eluted with 1.5 mol/L of ammonium acetate. Radioactivity was analyzed in a liquid scintillation counter.[11]

CASE REPORT

A 40-year-old white man with a history of chronic low back pain, depression, hypertension, and childhood asthma presented to the emergency department with shortness of breath, vomiting, and generalized abdominal discomfort. His medications included carisoprodol, hydrocodone/acetaminophen (paracetamol), metoprolol, candesartan, and rabeprazole sodium. He denied alcohol or intravenous drug use. On examination, his breathing was labored. Initial vital signs showed a temperature of 96.7°F, pulse rate of 126 beats/min, blood pressure of 138/88 mm Hg, respiratory rate of 36 breaths/min, and oxygen saturation of 99% on room air. His examination was unremarkable except for the presence of labored breathing. Arterial blood gas analysis showed a pH of 6.98, P_{CO_2} of 6 mm Hg, and P_{O_2} of 154 mm Hg. Serum bicarbonate level was 3 mEq/L (3 mmol/L). He was intubated in the emergency department and transferred to the medical intensive care unit. Hemoglobin level was 12.2 g/dL (122 g/L). Notably, serum amylase level was 1,127 U/L (normal, $\leq$100 U/L) and lipase level was 1,503 U/L (normal, 0 to 60 U/L). His other laboratory values are listed in Table 1. Computed tomography of the abdomen with oral contrast showed peripancreatic fluid and inflammation.

The patient was treated initially with isotonic bicarbonate containing intravenous fluids. Acetaminophen and carisoprodol were not administered during this or any subsequent admission. Serum bicarbonate levels and anion gap normalized during the next 3 days, and creatinine level returned to normal. After extubation, the patient was interviewed again and denied use of alcohol or other toxic substances. The patient signed out of the hospital against medical advice on hospital day 5.

Admission 2 was 26 days after day 1 of admission 1. The patient presented with dyspnea and fatigue. Medications included carisoprodol, hydrocodone/acetaminophen, candesartan, thiamine, and folate. Blood pressure was 88/44 mm Hg, and pulse rate was 140 beats/min. Physical examination was unremarkable. Laboratory data are listed in Table 1. Amylase and lipase levels were normal. He was treated with intravenous fluids, and his high anion gap metabolic acidosis and creatinine level were rapidly corrected. He was discharged 4 days after admission.

Admission 3 was 32 days after day 1 of admission 1. The patient again presented with dyspnea. Medications were unchanged from admission 2. Blood pressure was 81/63 mm Hg, and pulse rate was 117 beats/min. Laboratory data are listed in Table 1. He was administered intravenous fluids and again, his acidosis was corrected rapidly, with normalization of renal function. He was discharged quickly without a clinical diagnosis other than high anion gap metabolic acidosis.

Admission 4 was 46 days after day 1 of admission 1. The patient presented with fatigue and dyspnea, blood pressure of 121/73 mm Hg, pulse rate of 76 beats/min, and normal physical examination findings. Medications included amlodipine, candesartan, citalopram, metoprolol (Lopressor; Novartis, USA), pantoprazole, and hydrocodone/acetaminophen. Laboratory data and acidosis workup are listed in Table 1. He rapidly returned to baseline status with intravenous fluids and was discharged after 3 days with a diagnosis of high anion gap metabolic acidosis.

A urinary organic acid screen was sent from day 1 of admissions 3 and 4, and results with high 5-oxoproline levels were reported several days after the patient's fourth admission discharge. The patient's hydrocodone/acetaminophen combination was changed to hydrocodone/ibuprofen. Intermittent electrolyte panel results during the next 5 months were normal. Outpatient urinary organic acid screens showed normal 5-oxoproline levels and no elevation of other organic acids on 2 separate occasions. An extensive personal and family history was obtained from the patient, and there was no evidence suggesting occult inherited glutathione synthetase deficiency. He was not following a special diet. A

Table 1. Laboratory Data for 6 Hospital Admissions

Variable	Reference Interval	Admission 1	2	3	4	5	6
Arterial blood gas							
pH	6.98	7.11	7.12	7.32	7.24	7.08	
P_{CO_2} (mm Hg)	35-45	5	6	14	26	12	11
P_{O_2} (mm Hg)		99	140	140	114	117	131
Bicarbonate (mEq/L)	22-26	1	2	5	13	5	3
Serum							
Sodium (mEq/L)	135-145	144	142	141	136	140	141
Potassium (mEq/L)	3.5-5.1	4	7.3	5.8	5.3	4.6	4.9
Chloride (mEq/L)	98-106	109	111	110	103	107	101
Bicarbonate (mEq/L)	22-26	3	5	5	13	6	4
Urea nitrogen (mg/dL)	8-20	6	25	11	13	15	11
Creatinine (mg/dL)	0.7-1.2	1.6	1.9	1.4	1.2	1.2	2.3
Glucose (mg/dL)		209	120	115	92	143	165
Anion gap (mEq/L)		32*	26	26	20	27	36
Serum osmolality (mOsm/kg)		312	318	291	NA	NA	297
Acidosis workup							
Lactate (mg/dL)	0.5-2.2	4.3	4.6	3.7	1.5	1.6	5.2
Urine pH	5-9	5	5	5.5	5	5	5
Urine ketones (mg/dL)	Neg	40	40	Neg	Trace	Neg	Neg
Acetone	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Ethanol (mg/dL)	<0.5	<5	<5	<5	<5	<5	<5
Methanol (mg/dL)	<0.5	NA	Neg	Neg	Neg	NA	NA
Ethylene glycol (mg/L)	Neg	NA	Neg	Neg	Neg	NA	NA
Salicylate (mg/L)	5-25	<0.5	<0.5	<0.5	<0.5	NA	NA
Acetaminophen (μg/mL)	10-30	7.5	15.6	7.6	17.0	<2.0	4.1
Hippuric acid (g/L)	<0.8	NA	NA	<0.5	<0.5	NA	NA
D-Lactic acid (mmol/L)	<0.26	NA	NA	NA	<0.26	NA	NA
Urinary 5-oxoproline (mmol/mmol creatinine)	<0.06	NA	NA	20.7†	11.2†	NA	8.9‡

NOTE. To convert sodium, potassium, chloride, bicarbonate, and anion gap in mEq/L to mmol/L, multiply by 1.0; urea nitrogen in mg/dL to mmol/L, multiply by 0.357; creatinine in mg/dL to μmol/L, multiply by 88.4; glucose in mg/dL to mmol/L, multiply by 0.05551; osmolality in mOsm/kg to mmol/kg, multiply by 1.0; lactate in mg/dL to mmol/L, multiply by 0.111; ethanol in mg/dL to mmol/L, multiply by 0.217; methanol in mg/dL to mmol/L, multiply by 0.0312; ethylene glycol in mg/L to μmol/L, multiply by 16.11; salicylate in mg/L to mmol/L, multiply by 0.00724.

Abbreviations: Neg, negative; NA, not available.

*Anion gap calculation: Sodium – chloride – bicarbonate.

†Minor elevations of 3-hydroxybutyric, acetoacetic, lactic, 2-hydroxybutyric, 2-hydroxyisovaleric, and 2-hydroxyisocaproic acid noted.

‡Minor elevations of 3-hydroxyadipic acid, acetoacetic acid, lactic acid, 2-hydroxybutyric acid, 3-hydroxybutyric acid, 3-hydroxypropionic acid, 2-hydroxyisovaleric acid, and 4-hydroxyphenyllactic acid noted (Mayo Medical Laboratories).

homocysteine level was normal. There was no biochemical evidence of hemolysis.

Admission 5 was 5 months after admission 1. The patient presented with symptoms and signs of cholecystitis. Blood pressure was 152/95 mm Hg, and pulse rate was 120 beats/min. Medications included metoprolol, amlodipine, gabapentin, carisoprodol, citalopram, rabeprozole, and amitriptyline. Laboratory data are listed in Table 1. It is not clear whether the patient was using acetaminophen preadmission. He was treated with intravenous fluids and his acidosis resolved rapidly. He then underwent an uneventful cholecystectomy (with confirmed diagnosis of cholecystitis) and was discharged.

Admission 6 was 30 days after day 1 of admission 5. The patient presented with confusion and dyspnea. Blood pressure was 114/70 mm Hg, and pulse rate was 150 beats/min. His medications included valsartan, metoprolol, and folate, and he had resumed hydrocodone/acetaminophen at least 1 week before admission. Initial laboratory data and acidosis workup are listed in Table 1. His examination was unremarkable. He was treated with intravenous fluids and his acidosis and anion gap resolved quickly. He was discharged and again warned concerning the potential relationship of acetaminophen to his acidosis. The urinary organic acid screen later showed high levels of 5-oxoproline.

The patient reported that he has used no acetaminophen products since admission 6. During the ensuing year, he had 5 acute medical admissions (pneumonia once, asthma twice, and rabeprazole overdose with primary respiratory acidosis twice) without evidence of anion gap metabolic acidosis. Acetaminophen screen results were repeatedly negative.

During a period of no acute illness or evidence of 5-oxoprolinuria, the patient's blood was analyzed for glutathione synthetase activity (Table 2).

Table 2. Glutathione Synthetase Enzyme Activity

	Patient	Heterozygous GSD	Control
No. of patients	1	23	29
Level (pkatal*/mg hemoglobin)	8.8	3.1 (2.2-4.4)	6.3 (3.6-9.6)

Abbreviation: GSD, glutathione synthetase deficiency.
*Picomoles per second.

DISCUSSION

High anion gap metabolic acidosis is common in critically ill patients and only rarely presents a diagnostic dilemma regarding identification of the primary organic acid. As the anion gap increases, the more likely one is to identify the primary organic acid. Anion gaps of 25 to 29 mEq/L (25 to 29 mmol/L) and 30 to 45 mEq/L (30 to 45 mmol/L) will yield clearly defined organic acids 80% and 100% of the time, respectively.[12] However, it also is clear that there is often poor correlation between the level of anion gap and quantification of identifiable organic acids. In a study by Gabow et al,[12] measurable organic acids (including gas chromatographic-mass spectroscopic screening of serum or urine) accounted for only 62% (±28%) of the anion gap. This discrepancy is poorly understood and likely reflects multiple factors, including contributions of unidentified organic acids, changes in protein concentrations and their attendant charges, and effects of other nonacidic charged ions.[12]

Accumulation of 5-oxoproline is a rare cause of anion gap acidosis, but is characteristic of autosomal recessive glutathione synthetase deficiency.[1] Glutathione synthetase is a key enzyme in the γ-glutamyl cycle, in which 5-oxoproline is an intermediate metabolite (Fig 1). The cycle end product, glutathione, is involved in neutralizing toxic compounds through nonenzymatic and enzymatic reactions, the latter in conjunction with glutathione peroxidase. Glutathione synthetase deficiency can occur in a generalized form in which the clinical findings of jaundice, mental retardation, ataxia, seizures, hemolytic anemia, and anion gap metabolic acidosis with 5-oxoprolinuria present in the first few days of life. To date, there are more than 65 patients described with glutathione synthetase deficiency,[1] and likely many more patients are unreported.

The putative mechanism by which glutathione synthetase deficiency leads to 5-oxoprolinuria and acidosis derives from the observation that glutathione serves as a self-regulator by modulating substrate affinity of a precursor enzyme, γ-glutamylcysteine synthetase[13] (Fig 1). Activity of γ-glutamylcysteine synthetase is maintained with low glutathione levels, but normal or higher levels of glutathione directly downregulate the affinity of γ-glutamylcysteine synthetase for glutathione and thus limit further glutathione production. In glutathione synthetase deficiency, persistent low levels of glutathione maintain activation of γ-glutamylcysteine synthetase (by its affinity for glutathione) and, subsequently, ongoing synthesis of γ-glutamylcysteine. γ-Glutamylcysteine can be used directly as a substrate for γ-glutamylcyclotransferase (secondary metabolic pathway) and hydrolyzed to 5-oxoproline. 5-Oxoproline is oxidized to glutamate by 5-oxoprolinase. However, 5-oxoprolinase typically is the rate-limiting enzyme in the γ-glutamyl cycle; thus, high levels of 5-oxoproline may accumulate in blood and urine.[13]

There have been several recent reports of severe high anion gap metabolic acidosis secondary to 5-oxoproline that did not have clinical evidence for inherited disorders of the γ-glutamyl cycle.[2-9] After the initial report by Creer et al[2] in 1989, there have been approximately 20 reported cases.[3-9] Pitt and Hauser[5] described a series of 11 patients (aged 1 to 84 years) with high anion gaps, the majority with moderate or severe metabolic acidosis, and evidence of striking elevation of 5-oxoproline levels in urine, serum, or both. 5-Oxoproline was the predominant organic acid identified in each case.[5] All subjects had consumed acetaminophen (most in the therapeutic range), and all had elevation of hepatic transaminase levels in addition to a broad range of acute medical illnesses. In a second series by Dempsey et al,[7] 4 patients with acute high anion gap metabolic acidosis and high 5-oxo-

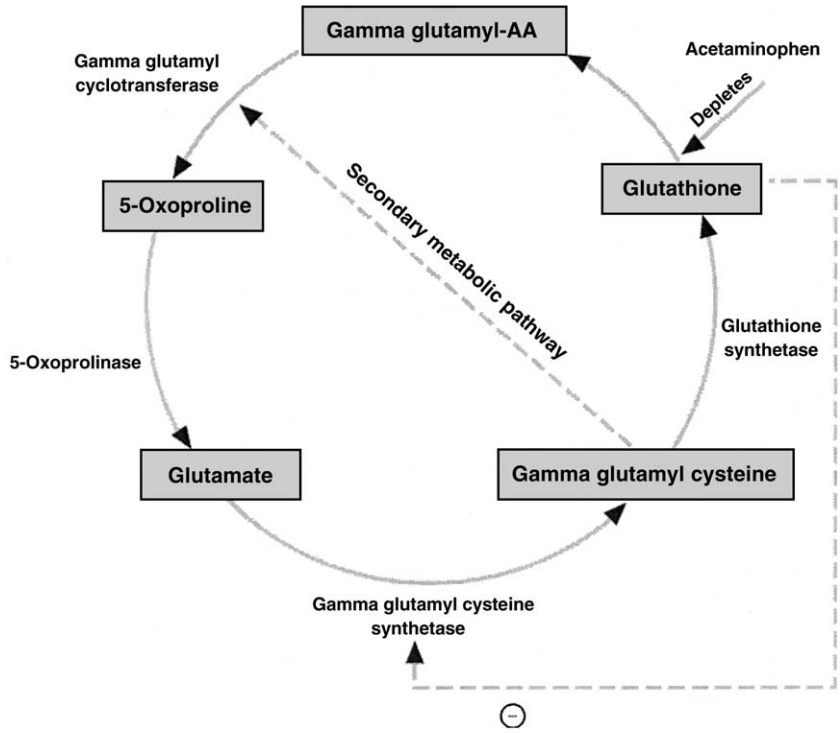

Fig 1. The γ-glutamyl cycle and secondary metabolic pathway for 5-oxoproline metabolism. The negative regulation of glutathione is indicated.

proline levels were reported. None had significant levels of other organic acids. Similar to the series by Pitt and Hauser,[5] all patients had evidence for acetaminophen ingestion and acute medical illnesses. Three patients had evidence for liver and kidney dysfunction, and 1 patient had clinical evidence of sepsis.[7] Bellary et al[8] reported a pregnant woman with type 1 diabetes with 2 episodes of anion gap acidosis, each without evidence of ketoacidosis or lactic acidosis. Elevated urinary 5-oxoproline levels were noted for the first episode, although the level was not reported. The patient reported an overdose of an acetaminophen compound (coproxamol), but acetaminophen level was undetectable.

The specific mechanism by which such patients without known hereditary defects develop this syndrome is puzzling and likely multifactorial. The capacity to generate sustained levels of 5-oxoproline without overt hereditary defects in the γ-glutamyl cycle appears, at a minimum, to include: (1) reduced glutathione levels depressing the usual feedback inhibition of γ-glutamylcysteine synthetase, (2) the metabolic potential of γ-glutamylcyclotransferase to enzymatically metabolize upregulated γ-glutamylcysteine synthesis directly to 5-oxoproline, and (3) production of 5-oxoproline in excess of its metabolism to glutamate by 5-oxoprolinase. Although other potential defects or altered pathways in the γ-glutamyl cycle might lead to increased 5-oxoproline production and high anion gap metabolic acidosis, none have been demonstrable from known regulation or defined inherited diseases of the γ-glutamyl cycle.

Secondary factors that transiently disrupt or alter normal metabolic pathways within the γ-glutamyl cycle are poorly understood in these adult patients. The potential role of acetaminophen is compelling and complex. Acetaminophen has been shown to enhance utilization of glutathione and promote depletion of glutathione stores.[14] However, normal cells are able to increase glutathione production when stressed by acetaminophen, and only at high concentrations of acetaminophen do glutathione stores become severely depleted and substantial cell toxicity become prominent.[15,16] Cells from patients with gluta-

thione synthetase deficiency are unable to replenish their already meager glutathione stores when stressed because of severe deficiency of glutathione synthetase. Not surprisingly, cells from patients who are heterozygous for glutathione synthetase deficiency contain approximately 50% of normal cellular glutathione levels when unstressed and have intermediate capacity between normal and glutathione synthetase deficiency cells when acetaminophen stressed, in terms of both cellular protection and the ability to replenish glutathione stores.[15,16] In other studies, 5-oxoprolinuria has been induced easily in rats fed a diet containing acetaminophen,[17] and, in studies of humans, 5-oxoprolinuria levels were significantly elevated in urine samples of patients administered acetaminophen compared with controls.[18] However, 1 patient in the study of Pitt and Hauser[5] was rechallenged with acetaminophen and did not develop organic aciduria, thus emphasizing that acetaminophen is only 1 possible critical cofactor. In our patient, 5 of 6 acidosis episodes were clearly associated with detectable acetaminophen levels.

Other potential factors involved in the generation of excess 5-oxoproline include relative deficiencies of glycine[19,20] or cysteine,[20] which are critical amino acids in the γ-glutamyl cycle. It also was observed that sepsis may lead to a generalized reduction in glutathione stores.[21] Other known causes of 5-oxoprolinuria include malnutrition and pregnancy (suspected limited availability of glycine),[22] artificial diets,[23] medications other than acetaminophen (vigabatrin, flucloxacillin, and netilmicin),[3,6] homocysteinuria (homocysteine substitutes for cysteine in the γ-glutamyl cycle),[24] severe burns and Stevens-Johnson syndrome,[25] preterm infants,[26] and other inherited disorders of metabolism, including urea cycle and tyrosine defects, GM_2 gangliosidosis, and decompensated states in propionic and methylmalonic acidemia.[25] None of these disorders leads to substantial levels of 5-oxoproline compared with glutathione synthetase deficiency or that seen in idiopathic or drug-associated cases, and other than the organic acidemias, none has been associated with a significant anion gap acidosis.

There are multiple defined enzyme deficiencies in the γ-glutamyl cycle and none, except for glutathione synthetase deficiency, has been associated with anion gap metabolic acidosis. However, there are approximately 8 reported cases of 5-oxoprolinase deficiency that had moderate elevations in urinary 5-oxoproline levels.[1] Although this enzyme deficiency would be expected to elevate 5-oxoproline levels, exceedingly high levels and acidosis have not been seen, likely because the production rate of 5-oxoproline appears normally regulated.

Individuals heterozygous for glutathione synthetase deficiency would be prime candidates for transient and potentially severe 5-oxoprolinuria with high anion gap metabolic acidosis given the known intermediate capacity of their cells (in vitro) for handling stress and toxic insults to the γ-glutamyl cycle.[15,16] Interestingly, there have been no reports of this phenomenon in families of patients with glutathione synthetase deficiency or from the 1 patient tested by Pitt et al[4] for glutathione synthetase or oxoprolinase activity. Our patient's glutathione synthetase activity clearly was in the normal range; thus, heterozygosity for glutathione synthetase deficiency was effectively excluded. A clearly defined factor for this syndrome of acquired 5-oxoprolinuria and high anion gap metabolic acidosis, other than exposure to acetaminophen or other reported drugs, remains elusive.

Given the ability of *N*-acetylcysteine to replenish glutathione stores in patients with acetaminophen toxicity, some investigators have suggested its use in patients with suspected 5-oxoprolinuria and high anion gap metabolic acidosis. Martensson et al[27] described beneficial effects of *N*-acetylcysteine in patients with inherited disease. Pitt and Hauser[5] described 2 acutely ill adults who developed high anion gap metabolic acidosis after administration of acetaminophen. These 2 patients were treated with intravenous *N*-acetylcysteine and had uneventful recoveries.[5] *N*-Acetylcysteine may be a reasonable treatment option in similar patients. However, the diagnosis of 5-oxoprolinuria usually is delayed and, second, the acidosis in our patient was corrected rapidly multiple times by simply withholding acetaminophen and administering bicarbonate-containing intravenous fluids.

In conclusion, we describe the first adult patient with recurrent 5-oxoprolinuria and high

anion gap metabolic acidosis unrelated to any known inherited disorder of the γ-glutamyl cycle and clearly excluded the possibility that our patient was heterozygous for glutathione synthetase deficiency. The concomitant use of acetaminophen related to his episodes of high anion gap metabolic acidosis and the absence of acidosis or evidence of 5-oxoprolinuria during long periods without acetaminophen greatly strengthens the association between acetaminophen use and acquired 5-oxoprolinuria and high anion gap metabolic acidosis. Alternative or coexistent mechanisms that may trigger this syndrome remain obscure. 5-Oxoprolinuria should be specifically considered in the differential for poorly explained high anion gap metabolic acidosis when measured levels of organic acids do not sufficiently account for their role in the anion gap and certainly when there is concurrent acetaminophen use.

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