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Am J Med Case Rep. Author manuscript; available in PMC 2019 August 12.

Published in final edited form as:

Am J Med Case Rep. 2019 ; 7(9): 200–202. doi:10.12691/ajmcr-7-9-5.

Recurrent Anion Gap Metabolic Acidosis

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Abstract

Background: Metabolic acidosis refers to any process that increases the hydrogen ions in the body and reduces the bicarbonate concentration. Metabolic acidosis is subdivided based on presence of anion gap (AG), and AG metabolic acidosis is most often due to ketoacidosis, lactic acidosis, renal failure, or toxic ingestions. AG metabolic acidosis is frequently encountered in the clinical practice. Rarely, the underlying cause of the AG metabolic acidosis is considered a diagnostic dilemma as the established algorithm allows the physicians to identify the etiology.

Case presentation: A fifty-three-year-old Black woman with well-controlled human immunodeficiency virus (HIV), hypertension, and asthma presented with recurrent episodes of severe anion gap metabolic acidosis. The patient's AG metabolic acidosis always corrected with the administration of intravenous normal saline. Laboratory studies were always negative for common causes of acidosis.

Conclusion: Nucleoside reverse transcriptase inhibitors-associated lactic acidosis has been reported in the literature. The shift to anaerobic mitochondrial metabolism induced by the HIV medications used in this patient could be explain the recurrent severe metabolic acidosis.

Keywords

anion gap; metabolic acidosis; recurrent metabolic acidosis; differential for metabolic acidosis; nucleoside reverse transcriptase inhibitors-associated lactic acidosis

1. Introduction

Acidosis refers to any process that leads to an increase in the serum hydrogen ion concentration while acidemia is defined as pH < 7.35 [1]. Acidosis can be further classified as metabolic vs. respiratory based on the underlying origin of insult. Respiratory and metabolic acidosis are related to changes in the carbon dioxide and bicarbonate respectively. Metabolic acidosis requires a bicarbonate level less than 24 and can be further subdivided based on the presence or absence of an anion gap [1,2].

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2. Case Presentation

A fifty-three-year-old African American female with a past medical history of HIV, hypertension, and asthma presented to the emergency room of our Institution with diffuse abdominal and bilateral lower extremity pain of one day-duration. The abdominal pain was described as crampy, knot-like, 9/10, and fluctuating in intensity with no radiation. The pain began the night before after eating a macaroni and cheese. Shortly after dinner, she had an episode of non-bloody, non-bilious vomiting. The next morning, the patient woke up with severe abdominal pain which prompted the arrival to the emergency department (ED). In the ED, the patient had a second episode of emesis. There was no associated fever, diarrhea, cough, weight loss, recent travel, sick contacts, changes in bowel movements, increased urinary frequency or history of diabetes, drug use or ingestion of toxic substances.

Patient has a history of multiple hospitalizations, ten within the last six years, for similar non-specific presenting complaints (consisting of abdominal pain and leg cramps) with anion gap metabolic acidosis of uncertain etiology that corrected within a few days of IV fluid administration and often sodium bicarbonate infusion. Only one admission was attributed to alcohol-induced acidosis and all of the other admissions were considered not be related to alcohol consumption.

Patient's past medical history was significant for HIV, maintained on emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey) for the past three years and emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera) for the last six years. She took amlodipine 10 mg daily for blood pressure control. Patient also reported having taken supplements containing potassium chloride, thiamine, and magnesium oxide, that were prescribed during previous hospital discharges for electrolyte deficiency.

Patient had no surgical history or known allergies. However, she reported a ten-year history of alcohol abuse (one vodka shot per day) that had ended three years ago. Patient denied current alcohol consumption, except for a glass of wine 2–3 times per year. She denied smoking and recreational drugs use. She was unemployed, living with her parents and used to take daily walks that lasted less than one hour. Her diet consists mainly of oatmeal, grilled cheese sandwiches, pasta, and chicken. She denies consuming any exotic products or supplements which would have contributed to her current state.

In the ED, her vital signs were within normal limits. Physical exam was unremarkable with a soft non-distended, non-tender abdomen and lower extremities with full range of motion and strength.

Laboratory studies were significant for severe metabolic acidosis (pH of 7.11) with an anion gap of 33 [142 – (103+6)] and bicarbonate of 6 mmol/L. Urinalysis was positive for ketones and urine toxicology screen was negative. Other results included blood urea nitrogen (BUN)/Creatinine of 21mg/dL/1.20mg/dL (baseline), total protein 10.4 g/dL, albumin 5.34 g/dL, alkaline phosphatase 137 Bodansky Units/L, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) 105 u/L/43 u/L, calcium 9.9 mg/dL, magnesium 1.8mg/dL, phosphorus 7.0 mg/dL, total bilirubin 2.0 mg/dL, and lactic acid 2.0 mg/dL. Patient had a normal white blood cell count, hemoglobin, platelet count, and coagulation profile.

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Normal saline (NS) was initiated and within fifteen hours, the bicarbonate was 12 mmol/L and the calculated anion gap was 17. She was admitted for further stabilization and work-up. On hospital day 2, additional tests were returned including beta-hydroxybutyrate 1.75 mmol/L, serum osmolality was 302 mOsm/kg and urine osmolarity was 710 mOsm/kg. Urine lytes were as follows: Sodium 203 mmol/L, potassium 24.6 mmol/L, and chloride 273 mmol/L. A right upper quadrant ultrasound demonstrated diffuse fatty infiltration of the liver.

The patient's laboratory results from previous hospitalizations are summarized in Table 1. Each hospitalization followed a very similar course. The patient would present to the emergency department with crampy abdominal or lower extremity pain, laboratory values revealing severe anion gap metabolic acidosis as high as 33 and pH as low as 7.05. Patient's discomfort and laboratory abnormalities corrected every time within 24 hours with only IV fluids with addition of bicarbonate on some occasions. Patient was usually released the following day with a normal anion gap. Urinalysis consistently revealed large ketones and work-up was negative for salicylates, acetaminophen, ethylene glycol, and ethanol. Interestingly, every admission was associated with multiple episodes of non-bloody, non-bilious (NBNB) vomiting. Patient reported 2–3 episodes of NBNB vomiting the prior three admissions but reported an average of 10–12 episodes of NBNB vomiting with the earlier admissions.

The index admission followed a similar trajectory as the patient recovered within 24 hours on IV normal saline as the anion gap decreased from 33 to 15 overnight. The bicarbonate improved from 6mmol/L to 12 mmol/L and the patient reported resolution of her symptoms by the next morning. To isolate possible causes, her home medications were held, and patient was only given IV normal saline. The patient was thoroughly interviewed before discharge to assess for any unusual dietary habits or psychiatric disease. Patient was emotionally stable and endorsed a normal, regular diet with exercise. She was discharged with the same home medications wand given close outpatient follow-up.

3. Discussion

Most causes of AG metabolic acidosis can be attributed to anaerobic metabolism and the resulting lactic acid accumulation [2]. Unmeasured anions increase the anion gap and disrupt the plasma neutrality created by sodium vs. bicarbonate and chloride. The standard causes of AG metabolic acidosis are represented with the pneumonic CAT MUDPILES: cyanide/carbon monoxide poisoning, arsenic, toluene, methanol/metformin, uremia, diabetic ketoacidosis, paraldehyde, iron/isoniazid, lactate, ethylene glycol, and salicylates [1,2,3].

Our patient presented with a history of recurrent AG metabolic acidosis. Although our patient had previously consumed alcohol, she denied drinking for the prior three years and her family confirmed that the patient led a healthy lifestyle, abstaining from alcohol, drugs, or any toxic substances. In addition, laboratory results were negative for alcohol except for one slight elevated admission recorded four years before. Therefore, ingestion of substances like methanol, ethylene glycol, salicylates, or paraldehyde as the cause of her acidosis were

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unlikely. Similarly, the mildly elevated lactic acid was likely secondary to a background etiology as slight elevations in lactic acid cannot explain this degree of acidosis.

Ketoacidosis is the most likely culprit in our patient who has consistently presented with urine ketones and has had elevated b-hydroxybutyrate. However, the etiology of the ketoacidosis remained unclear. Her normal blood glucose and hemoglobin $A1_c$ levels rules out the possibility of diabetic ketoacidosis [4]. The patient history and laboratory results did not suggest alcohol use and the patient endorsed leading a healthy lifestyle with a normal diet, eliminating the possibility of fasting ketosis or alcoholic ketoacidosis [5].

Non-diabetic ketoacidosis has been reported in lactating women [6]. These patients had severe metabolic acidosis which improved rapidly with carbohydrate intake and dextrose. Breastfeeding woman are more sensitive to ketoacidosis from low carbohydrate intake and starvation. Our patient was not breastfeeding and always reported a normal diet.

Recurrent cases of AG metabolic acidosis are rarely reported in the literature and the etiologies included episodic ethylene glycol ingestion, midazolam therapy, D-lactic acidosis secondary to short bowel syndrome, dialysis, pyroglutamic acid buildup associated with acetaminophen ingestion, and 5-oxoproline buildup secondary to glutathione synthetase deficiency [7–12]. While most of the above risk factors were negative in our patient, the possibility of an inborn error of metabolism is still possible and would need further investigation. Of note, our patient had been taking tenofovir for the past fifteen years. There has been reported cases of nucleoside reverse transcriptase inhibitors (NRTIs) associated lactic acidosis (NALA) [13,14]. The etiology of NALA involved mitochondrial toxicity, leading to impairment of mitochondrial aerobic metabolism and accumulation of lactic acid. The incidence of NALA is around 1% and it generally develops between 1 to 20 months after initiation of highly active antiretroviral therapy [13]. Given the timeline and recurrent nature, NALA although unlikely in our patient's case, could be contributing or triggering to the underlying acidosis.

4. Conclusion

AG metabolic acidosis is a commonly seen acid-base derangement and its etiology generally attributed to ketoacidosis, lactic acidosis, renal failure, or toxic ingestions. Recurrent causes of AG metabolic acidosis are rarely reported in the literature. We can hypothesize that the medications used to manage the underlying HIV disease could possibly explain the repeated episodes of anion gap metabolic acidosis. Nucleoside reverse transcriptase inhibitors-associated lactic acidosis has been reported in the literature, and the shift to anaerobic mitochondrial metabolism could be the reason for our patient's recurrent admissions for the severe metabolic acidosis.

Acknowledgements

This work is supported in part by Dr. Moro O. Salifu's efforts through NIH Grant # S21MD012474.

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Table 1.

Laboratory results for the ten hospital admissions – chronologically displayed - visit #10 was the index admission. Values with asterisks were obtained after the first day of admission

	Admissions										
Laboratory results	**Ref. values**	**1st**	**2nd**	**3rd**	**4th**	**5th**	**6th**	**7th**	**8th**	**9th**	**10th**
Venous blood gas											
pH	7.35–7.45	7.2	7.27	7.08	7.05	7.09	7.09	7.07	7.14	7.19	7.11
PCO2 (mm Hg)	35–45	25.4	29.6	23.1	23.4	27.2	22.5	27.5	27.5	36	20.8
PO2 (mm Hg)		32.2	42.7	56.3	26.5	39.6	45.4	30.7	45.7	35.8	61.6
Bicarbonate (mEq/L)	22–26	9.6	13.2	6.5	6.1	8.0	6.5	7.6	8.9	13.2	6.3
Serum											
Sodium (mmol/L)	136–145	145	140	137	143	139	145	143	142	140	142
Potassium (mmol/L)	3.5–5.1	5.1	4.4	5.4	5.2	6.3	5.5	4.9	5.2	5.8	6.5
Chloride (mmol/L)	98–107	110	108	102	106	103	108	112	105	104	103
Bicarbonate (mEq/L)	21–31	9	12	4	4	5	5	6	7	11	6
Urea Nitrogen (mg/dL)	7.0–25	24	16	20	14	21	20	14	27	12	21
Creatinine (mg/dL)	0.70–1.30	1.3	0.84	1.46	1.09	1.54	1.61	1	1.66	0.67	1.2
Glucose (mg/dL)	70–99	111	88	150	117	145	134	94	152	70	129
Serum Osm. (mOsm/kg)*		NA	NA	318	NA	337	339	318	NA	311	302
Anion gap (mEq/L)		26	20	31	33	31	32	25	30	25	33
Anion gap (within 24 hours)		13	12	15	15	13	16	13	11	12	15
Lactate (mmoles/L)	0.5–1.6	2.5	1.4	2.7	2.4	2.9	2.3	2.5	2.8	2.7	2
Urine pH	5.0–7.0	6.0	6.0	6.0	5.0	5	6	5.5	6	5	5
Urine ketones (mg/dL)	Neg	80	150	150	80	80	80	80	80	80	80
Acetest*	Neg	Large	Large	Large	Large	Large	Large	Moderate	Large	Large	Large
Ethanol (mg/dL)*	< 10.0	< 10.0	< 10.0	< 10.0	< 10.0	< 10.0	13	< 10.0	< 10.0	< 10.0	< 10.0
Salicylate (mg/dL)*	10.0–20.0	NA	NA	< 5.0	NA	NA	< 5.0	0	< 5.0	< 5.0	NA
Acetone*	Neg	NA	NA	Large	NA	Large	Large	Small	NA	NA	NA