Title

Non Anion Gap Metabolic Acidosis Induced During L-arginine Therapy in a Patient with Mitochondrial Encephalopathy Lactic Acidosis and Stroke (MELAS)

Journal

Proceedings of UCLA Health, 21(1)

Authors

Hanna, Ramy M.
Khorsan, Reza

Publication Date

2017-10-02

CLINICAL VIGNETTE

Non Anion Gap Metabolic Acidosis Induced During L-arginine Therapy in a Patient with Mitochondrial Encephalopathy Lactic Acidosis and Stroke (MELAS)

Ramy M. Hanna, MD and Reza Khorsan, MD

Introduction

Mitochondrial Encephalopathy Lactic Acidosis and Stroke (MELAS) is a rare mitochondrial DNA disease that is related to a family of mitochondrial diseases including MERRF syndrome (Myoclonal Epilepsy with Ragged Red Fibers) and Leber's Hereditary Optic Neuropathy (LHON). The genetic defect is in various components of proteins and transfer RNA molecules that are needed to make the NADPH dehydrogenase protein. The loss of these proteins results in failure of oxidative phosphorylation leading to increased fermentation and the buildup of lactic acidosis. Clinically the resulting symptoms are fatigue and stroke like symptoms for which the syndrome is named.[1]

L-arginine chloride was recently presented as a therapeutic agent for decreasing the duration of the stroke like symptoms that occur in MELAS.[2] Though the expected metabolic profile in MELAS is an anion gap lactic acidosis, we report a case where the primary biochemical anomaly was a non-anion gap metabolic acidosis. This was temporally related to starting L-arginine treatment. There was no diarrhea or other gastrointestinal losses, renal failure, or evidence of extra renal losses. Urinary anion gap was zero to negative but this is expected in the proximal tubular acidosis previously reported with L-arginine administration.

The mechanism of non-gap acidosis generation in L-arginine administration is due to an increase in serum chloride due to arginine metabolism. This mimics the hyperchloremia seen in non-gap metabolic acidosis.[3] In addition, arginine therapy has been associated with hyperkalemia. There have been known overdoses from arginine including a report in a 21 month-old infant.[4] There have also been reports involving L-arginine induced metabolic acidosis in patients receiving total parenteral nutrition (TPN).[5,6]

Case Report

Our patient is a 26 year-old female with history of developmental delay, hearing loss, history of several stroke like episodes, and chronic kidney disease (stage II-IIIa, eGFR 60-70 ml/min). She developed status epilepticus at an outside hospital and was started on depakote and phenytoin. MRI showed multifocal edema and MELAS was considered among several items on the differential diagnosis. An elevated lactate/pyruvate ratio detected on cerebrospinal fluid exam increased concern for MELAS. The patient was given IV normal saline and when suspicion increased for diagnosis, she was started on L-Arginine load, followed by 5 days of continuous infusion of L-arginine.

Initially the patient's serum bicarbonate was 23 mmol/L, with a borderline anion gap of 15, lactate level was 16 mg/dL (within normal limits). Her serum bicarbonate continued to drop to a nadir of 10 after the 5 days of L-arginine loading and continuous infusion, and her anion gap remained within normal limits. Her venous blood gas analysis did not show a respiratory alkalosis that could cause compensatory metabolic changes with partial pressure of PCo2 in venous blood of 40 mmHg. Her pH was quite acidotic at 7.13.

Discussion

The patient's expected PCO2 was calculated to be 23-25 mmHg by the Winter's formula in case of metabolic acidosis (1.5x [sHCo3]+8 +/- 2). Her pH of 7.13 was severely low given the fact that she suffered from a non-gap metabolic acidosis as well as a lack of respiratory compensation acting as a de-factor respiratory acidosis in addition.

Her anion gap as calculated by (sNa-(sHCo3+sCl)) dropped from 15 at outset to 10-12 during L-arginine infusion, which strongly suggests that a non-gap process was causing acidosis rather than a gap acidosis etiology like lactic acidosis. The available reports suggested that L-arginine can cause a proximal tubular acidosis, with some reports showing a fanconi's syndrome like pattern.[7] A urine anion gap uAG was obtained and was -7 which was negative as expected as uAG are not usually positive in proximal renal tubular acidosis. Unlike other reports of hyperkalemia with arginine infusion (due to acidosis or other metabolic effects of L-arginine administration), the patient's serum potassium remained normal throughout administration of L-arginine. The patient had briefly received IV normal saline prior to L-arginine administration, but the acidosis did not abate with it being stopped, again suggesting that the patient had a proximal renal tubular acidosis due to L-arginine administration.
We present a complex acid-base state that initially could have been dismissed as lactic acidosis, when a closer examination reveals it is due to a metabolic side effect of a rarely used medication used in a rare genetic disorder. The patient's acid

base state is most correctly a non-gap metabolic acidosis with mixed concomitant respiratory acidosis due to lack of compensatory decrease in the partial pressure of CO2 (PCO2). Ultimately, the timing, biochemistry, and analysis of urinary electrolytes confirm this finding. The lack of an elevated serum lactic acidosis shows that L-Arginine while helpful in mitigating stroke like symptoms, may, inadvertently worsen or cause another acidosis overlaying that that can be seen in MELAS cases. See Figure 1 for graphs of serum potassium, anion gap, creatinine, bicarbonate, and delta gap (24-sHCo3) plotted against timing of L-arginine administration.

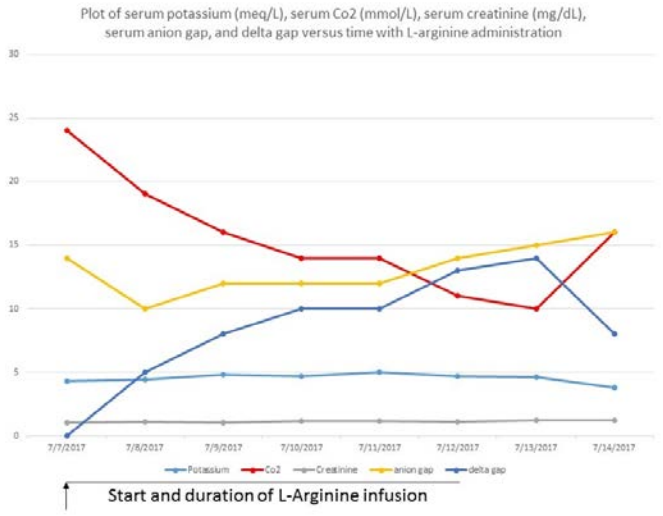

Figure 1: Plot of serum potassium (meq/L), serum Co2 (mmol/L), serum creatinine (mg/dL), serum anion gap, and delta gap versus time with L-arginine administration. Arrow start of L-arginine infusion, line continuation of L-arginine infusion from 7/7/2017 to 7/12/2017.

REFERENCES

1. **Koga Y, Akita Y, Nishioka J, Yatsuga S, Povalko N, Tanabe Y, Fujimoto S, Matsuishi T**. L-arginine improves the symptoms of strokelike episodes in MELAS. *Neurology*. 2005 Feb 22;64(4):710-2. PubMed PMID: 15728297.
2. **Batshaw ML, MacArthur RB, Tuchman M**. Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr*. 2001 Jan;138(1 Suppl):S46-54; discussion S54-5. Review. Erratum in: J Pediatr 2002 Apr;140(4):490. PubMed PMID: 11148549.
3. **Pedrinelli R, Ebel M, Catapano G, Dell'Omo G, Ducci M, Del Chicca M, Clerico A**. Pressor, renal and endocrine effects of L-arginine in essential hypertensives. *Eur J Clin Pharmacol*. 1995;48(3-4):195-201. PubMed PMID: 7589041.
4. **Gerard JM, Luisiri A**. A fatal overdose of arginine hydrochloride. *J Toxicol Clin Toxicol*. 1997;35(6):621-5. PubMed PMID: 9365430.
5. **Kalogiannidou E, Passadakis P, Panagoutsos S, Mavromatidis K, Vargemezis V**. Effects of parenteral infusion of amino acid solutions in acid-base balance in patients with advanced chronic renal failure. *J Nephrol Therapeutic*. 2011;S3:004.
6. **Heird WC, Dell RB, Driscoll JM Jr, Grebin B, Winters RW**. Metabolic acidosis resulting from intravenous alimentation mixtures containing synthetic amino acids. *N Engl J Med*. 1972 Nov 9;287(19):943-8. PubMed PMID: 4627861.
7. **Batlle D, Hays S, Foley R, Chan Y, Arruda JA, Kurtzman NA**. Proximal renal tubular acidosis and hypophosphatemia induced by arginine. *Adv Exp Med Biol*. 1982;151:239-49. PubMed PMID: 6817609.

Submitted October 2, 2017