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Case Report

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A Challenging Metabolic Acidosis Management in a Young Patient with Transalodase Defeciency, T1DM, and pRTA

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Transaldose; Hepatosplenomegaly; Diphosphate

1. Abstract

1.1. Objective: To enhance the effectiveness and confidence in treating patients with rare metabolic disorders complicated by even more complex presentation.

1.2. Case: We report a rare case of a 14-year-old girl with Eyaid Syndrome – Transaldose deficiency 1,2 (OMIM 606003) based on both clinical and molecular finding of homozygous pathogenic variant in TALDO1 gene, c 793del p. (Gin265Argfs*56).

She developed type 1 diabetes at around the age of nine years; by that ti me she was found to have a baseline non-inion gap metabolic acidosis that was persistent despite adequate management of her diabetes. Extensive work up for possible renal causes -giving that they are part of her primary syndrome– revealed proximal renal tubular acidosis.

Upon one ER visit; she presented with abdominal pain, voming, diarrhea, and lethargy, labs showed metabolic acidosis with PH of 6.93, HCO3 of 3.3 only, and here begins her challenging management approach.

1.3. Conclusion: Our patient has responded to sodium bicarbonate excellently in a well monitored clinical and biochemical settings, however a more large-scale literature review for all involved subspecialties and report of such challenging cases is inevitably needed for an evidence based clinical practice in managing patients with rare metabolic conditions.

2. Introduction

Transaldolase deficiency (TALDO-D, Eyaid syndrome, OMIM 606003) is a rare autosomal recessive inborn error of the pentose phosphate pathway first described in 2001 (Verhoeven et al. 2001). Patients can present either prenatally, with intrauterine growth restriction (IUGR) and/or oligohydramnios; in the neonatal period, with dysmorphic facial features, cardiovascular defects, hepatosplenomegaly, anemia, and thrombocytopenia; or later in life, with a milder phenotype [1,2].

A defect of TALDO in the pentose phosphate pathway not only has an effect on organogenesis but also on the function of organ systems after birth. Transaldolase is an important enzyme in the PPP, and its deficiency has been shown to deplete NADPH, glutathione (GSH), and diminish nitric oxide (NO) production, lead to decreased mitochondrial transmembrane potential and mitochondrial mass and reduced adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio in the liver of TALDO1−/− mice (Hanczko et al. 2009). In fibroblast and lymphoblast cell lines from a TALDO-D patient, the nucleotides NADPH and NAD + were also depleted, while ADP-ribose had accumulated. A diminished mitochondrial transmembrane potential was also present, but there was an increased mitochondrial mass, which was associated with increased NO, ATP, and Ca2+. Also, enhanced apoptosis was detected (Qian et al. 2008). Failure to recycle ribose-5P through the nonoxidative branch, and conversion of C5 sugar phosphates to C5 sugars to C5 polyols converting NADPH to NADH + results in decreased NADPH necessary for reductive biosynthesis (such as lipid synthesis, cholesterol synthesis, and fatty acid chain elongation) and leads to secondary depletion of GSH and increased oxidative stress. It thus seems expected that the

liver (detoxification and synthesis) and bone marrow (hematopoiesis) are the organs most affected.

Accumulation of the potentially toxic sugar-phosphate (sedoheptulose-7P) and/or polyols (erythritol, arabitol, ribitol, sedoheptitol, perseitol) and C7 sugars (mannoheptulose and sedoheptulose) might result in liver damage, as has been shown in patients with galactosemia in whom galactose-1P and galactitol accumulate [1].

Demand for the PPP is highest in the liver, and the liver is the organ with the highest enzyme activity next to the kidney (James et al. 1985). Kidney involvement is also one of the most common abnormalities in this patient cohort. Kidney problems reported are mainly tubular dysfunction (high energy demand), where loss of calcium is one of the main features (tubulopathy), possibly even leading to nephrocalcinosis or kidney stones. Although symptoms occur in organs with the highest TALDO enzyme activity, there seems to be no correlation between residual enzymatic activity and clinical outcome [1].

3. Case and Discussion

We report a rare case of a 14-year-old girl with Eyaid Syndrome – Transaldose deficiency,2 (OMIM 606003) based on both clinical and molecular finding of homozygous pathogenic variant in TALDO1 gene, c.793del p. (Gin265Argfs*56).

She developed type 1 diabetes at around the age of nine years, by that time she was found to have a baseline non-inion gap metabolic acidosis that was persistent despite adequate management of her diabetes. Extensive work up for possible renal causes -giving that they are part of her primary syndrome- Proximal and distal RTA was found in up to 29% of patients in the largest retrospective study of 34 patient [1] – revealed proximal renal tubular acidosis evident by increased urinary excretion of amino acids, glucose, and phosphate along with normal renal ultrasound. She also had developmental delay and progressive liver failure resulting in cirrhosis, portal hypertension and esophageal varices.

Upon one ER visit; she presented at 3:00 am with one day history of mild abdominal pain, vomiting, diarrhea and lethargy, labs showed metabolic acidosis with VBG as follows: pH 6.93, HCO3 3.3, K 3.8, N 136 and Chloride of 118, AGAP 14.7, Delta ratio 7.5 / 20.7, and here begins her complex management challenge.

Her metabolic acidosis could be related to her underlying pRTA, missed insulin and sodium bicarbonate dosage, the acute illness itself (viral gastroenteritis); Making the diagnosis and management challenging to identify which of them is the major contributor to her acidosis, and what would be the best course of action? when to stop her insulin infusion and when to start sodium bicarbonate for which we will highlight in this case report.

Normal serum anion gap is measured from the addition of HCO_{3-} + Cl^- then subtracting the serum Na+ in the same blood sample [4-7]. Variations in normal anion gap may have a big range from 3 to 11, and 8 to 16 mEq/L [10-11] depending on the lab instrument used.

Delta ratio [3] is a simple tool that can be used for evaluating metabolic acidosis to figure out if the biochemical derangement might be cause by a pure high AG metabolic acidosis or if the patient is having a simultaneous normal AG metabolic acidosis [3-8]. It is calculated as:

[(Calculated (AG) – 12) / (24 – serum bicarbonate)] [3,13], with 12 as normal AG and 24 as the accepted normal value for serum bicarbonate [3,9,13]. As mentioned previously; calculation of AG using [Na – (Cl + HCO3)] [3].

Assuming that serum bicarbonate is the sole buffer for extracellular fluid compartment. In a specific case of metabolic acidosis, any increase in AG should be matched by a decrease in the serum bicarbonate, and thus the ratio should be around 1, Again, this is assuming that serum bicarbonate is the only buffer [9].

Since mixed acid-base disorders would be suspected if Delta gap is < 0.8 or > 1.2 [3,14]. This method can be helpful as one element to help analyze the pathophysiology behind her acidosis14. However as this shouldn't be taken in the context of the patient condition overall, knowing its limitations [4,5,13,15]. The ratio might be > 1.2 [3,14,15] in cases of chronic respiratory alkalosis.

However, once delta ratio is calculated, and found to be between 0.3 and 0.7 then normal AG metabolic acidosis might be implicated in the acidosis, and this would lead the clinician to dig deeper into the possible differential of the case [3].

Back to our patient, Delta Ratio was [(14.7 - 12)/ (24 – 3.3)] = 7.5/20.7 = 0.36 which is suggestive of an ongoing NAGMA, due to pRTA, in addition to the expected HAGMA due to DKA.

This has led to our suggestion to start her back on serum bicarbonate immediately, back to her daily replacement dose alongside her insulin therapy. However, due to the concern from the Pediatric ICU team, this was delayed.

Her investigations with timing of start of bicarbonate were:

Initial ER VBG,

pH 6.93, HCO3 3.3, PCO2 12 at 4:00 am.

pH 6.96, HCO3 3.1, BE -27.1, at 07:43.

pH 7.00, HCO3 6.2, BE -23.7, at 10:10.

pH 7.06, HCO3 5.2, BE -23.3, at 12:22.

pH 7.16, HCO3 5.1, BE -21.4, at 14:04.

pH 7.12, HCO3 6.6, BE -20.7, at 16:17.

Bicarbonate was started at around 16:30 [Q6 hrly, 40 meq, Wt:21.7, 7.3 meq/kg/day] which has resulted in significant clinical, and biochemical improvement, in contrast to her minimal improvement once insulin infusion was started.

pH 7.29, HCO3 7.8, BE -16.6, at 23:41.

pH 7.34, HCO3 11, BE -13.1, at 03:56.

The patient gradually returned to her baseline, showed good activity, fully oriented, her appetite improved, she was put on an insulin sliding scale till she was back on SC doses, she was sent home in good clinical state, along with adjustment of her sodium bicarbonate dose with close Endocrine, and Nephrology follow up.

Thorough instruction was provided for her and her family on the importance of medication compliance and educated for concerning symptoms to present to the ER.

She has responded to sodium bicarbonate excellently in a well monitored clinical and biochemical settings, however a larger-scale literature review for all involved subspecialties and report of such challenging cases is crucially needed for an evidence based clinical practice in managing such patients.

4. Conclusion

We here by conclude that is is challenging to treat such patients with combined metabolic acidosis, in her case the pRTA, DKA, plus a stressful, infecous trigger; All of which have contributed to her marked acidosis. Sodium bicarbonate may complicate patients with DKA resulting in cerebral edema, along with its other SE of electrolyte and metabolic derangement if not used accurately, while at the same time it is a crucial part in managing her pRTA, hence; clinical judgement with close monitoring and the use of constellation of clinical status, laboratory finding along with accurate calculation of supportive equations to guid clinical decision and management. Further review is needed to revisit such presentation and it would be of great help to share similar experiences from expertise in order to facilitate best management and outcome for patients with rare hereidatory conditions.

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