CASE REPORT

A challenging metabolic acidosis management case in a young patient with transaldodase defeciency, T1DM, and pRTA

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ABSTRACT

Background: Transaldolase deficiency (TALDO-D, Eyaid syndrome) is a rare autosomal recessive disorder of the pentose phosphate pathway. It can present prenatally with intrauterine growth restriction or oligohydramnios; neonatally with dysmorphic features, cardiovascular defects, hepatosplenomegaly, anemia, and thrombocytopenia; or later with a milder phenotype. The present case report aimed at enhancing the effectiveness and confidence in treating patients with rare metabolic disorders that are further complicated by complex presentation.

Case Presentation: We present a rare case of a 14-year-old girl diagnosed with Eyaid Syndrome - TALDO-D based on clinical and molecular findings of a homozygous pathogenic variant in the *TALDO1* gene, c.793del, p.(Gln265Argfs*56). She developed type 1 diabetes around the age of nine and was found to have a baseline non-anion gap metabolic acidosis that persisted despite adequate diabetes management. An extensive workup for possible renal causes, given that they are part of her primary syndrome, revealed proximal renal tubular acidosis. During an emergency department visit, she presented with abdominal pain, vomiting, diarrhea, and lethargy. Laboratories showed severe metabolic acidosis (pH of 6.93, $HCO3^-$ of 3.3), marking the beginning of her challenging management approach.

Conclusion: The patient in this case report has shown an excellent response to sodium bicarbonate in a well-monitored clinical and biochemical setting. However, given the rarity and complexity of such cases, it is imperative to conduct a comprehensive literature review involving all relevant subspecialties and report similar challenging cases to establish evidence-based clinical practices for the high-quality management of this rare patient population.

Keywords: Transaldolase deficiency, mixed metabolic acidosis, DKA, RTA.

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 (1). Patients can present prenatally with intrauterine growth restriction and/or oligohydramnios; in the neonatal period, with dysmorphic facial features, cardiovascular defects, hepatosplenomegaly, anemia, and thrombocytopenia; or later in life, with the milder phenotype (2,3).

A defect in TALDO enzyme in the pentose phosphate pathway affects not only organogenesis but also organ function after birth. Transaldolase is a key enzyme in this pathway, and its deficiency has been shown to deplete NADPH and glutathione (GSH) and reduce nitric oxide (NO) production. This leads to decreased mitochondrial transmembrane potential, reduced mitochondrial mass, and a lowered ATP/ADP ratio in the liver of *TALDO1*–/–

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mice (4). In fibroblast and lymphoblast cell lines from a TALDO-D patient, nucleotides NADPH and NAD+ were also depleted, while ADP-ribose accumulated. A diminished mitochondrial transmembrane potential was observed, but mitochondrial mass increased, associated with elevated NO, ATP, and Ca^{2+} levels. Enhanced apoptosis was also detected.

Failure to recycle ribose-5P through the non-oxidative branch, converting C5 sugar phosphates to C5 sugars, results in decreased NADPH, necessary for reductive biosynthesis (e.g., lipid synthesis, cholesterol synthesis, and fatty acid elongation). This leads to secondary depletion of GSH and increased oxidative stress. Consequently, the liver (detoxification and synthesis) and bone marrow (hematopoiesis) are the most affected organs. Accumulation of toxic sugar-phosphates (e.g., sedoheptulose-7P) and/or polyols (e.g., erythritol, arabitol, ribitol, sedoheptitol, and perseitol) and C7 sugars (e.g., mannoheptulose and sedoheptulose) may result in liver damage, similar to what is observed in patients with galactosemia, where galactose-1P and galactitol accumulate (2).

The pentose phosphate pathway is most active in the liver, which has the highest enzyme activity, followed by the kidney. Kidney involvement is common in this patient cohort, mainly manifesting as tubular dysfunction, which has high energy demands. Calcium loss (tubulopathy), possibly leading to nephrocalcinosis or kidney stones, is a key feature. Although symptoms occur in organs with the highest TALDO enzyme activity, there seems to be no correlation between residual enzymatic activity and clinical outcomes (2).

Case Presentation and Discussion

We report a rare case of a 14-year-old girl with Eyaid Syndrome - TALDO-D (OMIM 606003), confirmed molecularly using single-gene sequencing, which revealed a homozygous pathogenic variant in the *TALDO1* gene, c.793del, p.(Gln265Argfs*56). She developed type 1 diabetes around the age of nine, at which time she was found to have a baseline non-anion gap metabolic acidosis that persisted despite adequate diabetes management. An extensive workup for possible renal causes given that they are part of her primary syndrome revealed proximal renal tubular acidosis (pRTA), evidenced by increased urinary excretion of amino acids, glucose, and phosphate, along with a normal renal ultrasound. Proximal and distal RTA was found in up to 29% of patients in the largest retrospective study of 34 patients (2). She also had developmental delay and progressive liver failure, resulting in cirrhosis, portal hypertension, and esophageal varices.

During the emergency department visit, she presented was presented at 3:00 am with a 1-day history of mild abdominal pain, vomiting, diarrhea, and lethargy. Laboratories showed metabolic acidosis with the following VBG results: pH 6.93, $HCO3^-$ 3.3, K 3.8, Na 136, and chloride 118. Anion gap (AG) was 14.7, the delta ratio was 7.5/20.7, and here began her complex management challenge. Her metabolic acidosis could be related to her underlying pRTA, missed insulin and sodium bicarbonate dosage, or the acute illness itself (e.g., viral gastroenteritis). This made the diagnosis and management challenging, as it was difficult to identify which factor was the major contributor to her acidosis, and what would be the best course of action. Key questions arose, such as when to stop her insulin infusion and when to start sodium bicarbonate, which we will highlight in this case report.

Normal serum AG is calculated by adding $HCO3^-$ and Cl^-, then subtracting this total from the serum Na+ in the same blood sample (5-8). Variations in the normal AG can range from 3 to 11 mEq/l or 8 to 16 mEq/l, depending on the laboratory instrument used (9,10). The delta ratio (3) is a simple tool for evaluating metabolic acidosis to determine if the biochemical derangement is caused by pure high AG metabolic acidosis or if the patient has simultaneous normal AG metabolic acidosis (9,10). It is calculated as follows:

(Calculated (AG) - 12) / (24 - serum bicarbonate) (11,9), with 12 as normal AG and 24 as the accepted normal value for serum bicarbonate (11,12,9). As mentioned previously; calculation of AG using [Na – (Cl + HCO_3–)].

This calculation assumes that serum bicarbonate is the sole buffer for the extracellular fluid compartment (11). In the case of metabolic acidosis, any increase in AG should be matched by a decrease in serum bicarbonate, resulting in a ratio of around 1. Mixed acid-base disorders would be suspected if the delta ratio is <0.8 or >1.2 (11,12,13). This method can help analyze the pathophysiology of acidosis, though it should be used in conjunction with the patient's overall condition, keeping its limitations in mind (5,6,9). The ratio may be >1.2 (11,8) in cases of chronic respiratory alkalosis. If the delta ratio is calculated and found to be between 0.3 and 0.7, normal AG metabolic acidosis may be implicated, leading the clinician to explore further differentials (11). . In our patient, the delta ratio was (14.7-12)/(24-3.3)(14.7-12)/(24-3.3)(14.7-12)/(24-3.3) = 7.5/20.7 = 0.36, which is suggestive of ongoing Normal Anion Gap Metabolic Acidosis (NAGMA), due to pRTA, in addition to the expected High Anion Gap Metabolic Acidosis (HAGMA) due to diabetic ketoacidosis (DKA). This led us to suggest resuming sodium bicarbonate immediately, at her daily replacement dose, alongside her insulin therapy. However, due to concerns from the Pediatric ICU team, this was delayed.

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. 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 subcutaneous doses, and she was sent home in a good clinical state, along with adjustment of her sodium bicarbonate dose with close endocrine, and nephrology follow up (Table 1).

Table 1. Treatment strategy.

Initial VBG	Post bicarbonate treatment (Q6 hrly, 40 meq, Wt:21.7, 7.3 meq/kg/day)
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	pH 7.29, HCO3– 7.8, BE -16.6, at 23:41 pH 7.34, HCO3– 11, BE -13.1, at 03:56

Thorough instruction was provided for her and her family on the importance of medication compliance and education concerning symptoms to present to the emergency department. She responded to sodium bicarbonate excellently in 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 evidence-based clinical practice in managing such patients.

Conclusion

We conclude that it is challenging to treat such patients with combined metabolic acidosis, in the present case the pRTA, DKA, plus a stressful, infectious trigger; All of which have contributed to her marked acidosis. Sodium bicarbonate may complicate patients with DKA resulting in cerebraledema, along with its other side effects 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 judgment with close monitoring and the use of a constellation of clinical status, laboratory finding along with accurate calculation of supportive equations to guide clinical decision and management. Further studies are needed to revisit such presentation and it would be of great help to share similar experiences from expertise to facilitate best management and outcome for patients with rare hereditary conditions.

Declaration of conflicting interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for publication

Informed consent was obtained from the parents of the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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