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Proximal renal tubular acidosis manifesting as severe sepsis and hypernatremic dehydration

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Summary
Renal tubular acidosis(RTA) type 2 in new-borns is an inherited/acquired disorder that impairs the kidney's ability to absorb filtered bicarbonate[1]. It is characterized by normal anion gap (hyperchloremic)metabolic acidosis with low urine pH[3]. We describe the case of a term male new-born who was referred to the NICU with lethargy and refusal to feed. The sepsis screen was positive, so antibiotics were given based on culture and sensitivity(Staphylococcus hominis). There were no ambiguous genitalia and no signs of adrenal insufficiency. The neonate's clinical condition worsened despite proper antibiotics, therefore a repeat sepsis screen and ABG were performed, which revealed hypernatremia, normal anion gap metabolic acidosis, hypokalaemia, and increased serum osmolality. The metabolic condition did not improve despite proper fluid and electrolyte therapy. Urine electrolytes revealed a positive anion gap and pH<5.5. To confirm proximal RTA, a bicarbonate loading test was done[3]. The fractional excretion of bicarbonate was measured, and a value>15mEq/L confirmed the diagnosis[3]. The patient was administered 1mEq/kg NaHCO3 for 3 days and repeat ABGs revealed gradual resolution of metabolic acidosis and hypernatremia. The daily dose of sodium bicarbonate was raised to 5mEq/Kg. The infant gradually recovered and was discharged on oral supplements.

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I. Introduction

Bicarbonate is readily filtered and has a similar concentration in the glomerular filtrate as in plasma(25 mEq/L)[1]. Approximately 80% of filtered HCO3 is reabsorbed by the proximal tubule, while the remaining 20% is recovered by the loop of Henle, distal tubules, and collecting tubules[5]. A defect in HCO_3 reabsorption in the proximal tubule causes a larger quantity of filtered HCO_3 to be delivered to the distal segments, causing urinary HCO_3 wastage[5]. Here, we present the case of a neonate who presented with sepsis and hypernatremic dehydration and was later diagnosed with type 2 renal tubular acidosis.

II. Case Presentation

A male neonate was admitted to the emergency room with refusal to feed and lethargy. The CRT was< 3 seconds and BP was within the 50th to 95th centile. The sepsis screen done at presentation was positive, and the blood culture showed the presence of *Staphylococcus hominis* sensitive to amikacin. Lumbar puncture was within normal limits and cultures were sterile. There were no ambiguous genitalia. The neonate's clinical worsening (refusal to feed, lethargy, and persistent regurgitation of feed and, tachypnoea) despite antibiotics prompted a second sepsis screen and ABG after 5 days. The second sepsis screen was negative and ABG was suggestive of hypernatremia(Na^+-156mEq/l) with normal ion gap metabolic acidosis and increased serum osmolality. Considering, hypernatremic dehydration with a hypotonic fluid deficit, the urine sodium, and urine osmolality were sent. The Urinary sodium was 240.0 mmol/l(>20 mmol/), urine osmolality was 519.09mosmole/kg(<700mosm/L) indicating a renal hypotonic fluid loss[2]. The fluid was given at 125% maintenance. Despite fluid replacement and sodium restriction, repeat ABG consistently showed normal anion gap metabolic acidosis with hypernatremia with raised plasma osmolality and no clinical improvement. Urine electrolytes were done to determine the urine anion gap ($Na^+ + K^+ - Cl^-$) which was positive, pH<5.5, with normal serum urea and creatinine, indicating the possibility of proximal RTA thereby shedding light on the obscurity[3].

INVESTIGATIONS

The sepsis screen (CRP/µESR/I:T ratio/ANC) done at the time of hospitalization was positive[6], and the blood culture showed the presence of *Staphylococcus hominis* sensitive to amikacin. Sensitive antibiotics

were started, and a lumbar puncture was done after taking consent from the parents. The routine microscopy was within normal limits and cultures were sterile. The neonate's clinical worsening despite antibiotics prompted a second sepsis screen and ABG. The second screen was negative and the ABG was suggestive of hypernatremia (Na^+-156mEq/l) with normal ion gap metabolic acidosis with hypokalaemia and increased serum osmolality. Considering, hypernatremia dehydration with a hypotonic fluid deficit, the urine sodium, and urine osmolality were sent. The Urinary sodium was 240.0 mmol/l (>20 mmol/) and Urine osmolality was 519.09mosmole/kg (<700mosm/L) indicating a renal hypotonic fluid loss[2]. Urine electrolytes were done to determine the urine anion gap(Na^++K^+- Cl^-) which was positive, pH<5.5, and normal serum urea and creatinine, indicating the possibility of proximal RTA[3]. USG whole abdomen did not show any signs of nephrocalcinosis[3]. Vitamin D levels were insufficient(14ng/ml) and hypocalcemia was never documented during hospitalization. Urine for glucose was positive and proteins were negative[3]. Plasma concentrations of glucose and amino acids were normal. The fundus examination was done to rule out cataract, glaucoma, and band keratopathy, and was normal[3]. Whole exome sequencing was also done for Dent and Lowe's syndrome, and it was normal[3].

DIFFERENTIAL DIAGNOSIS

The neonate presented with features of sepsis- lethargy, and refusal to feed. Initially, the patient was managed as a case of late-onset sepsis[6]. The blood culture was positive *(Staphylococcus hominis)* sensitive to amikacin.There were no ambiguous genitalia and no signs of adrenal insufficiency. ABG revealed hypernatremia with normal ion gap metabolic acidosis with hypokalaemia and increased serum osmolality. Considering hypernatremic dehydration, the patient was given 0.9% NS bolus 20ml/kg over 20 minutes followed by maintenance fluid (D5 N/2 saline with 20mEq/L KCL) at 125%[2].

The metabolic condition did not improve despite appropriate fluid and electrolyte therapy. Urine electrolytes revealed a positive anion gap and pH<5.5. To confirm proximal RTA, a bicarbonate loading test was done. The fractional excretion of bicarbonate was measured, and a value>15mEq/L confirmed the diagnosis[3]. Whole exome sequencing was also done for Dent and Lowe's syndrome however, it was normal.

TREATMENT

Initially, the patient was treated as a case of late-onset sepsis and antibiotics cefotaxime and amikacin were started. The patient was orally allowed and kept on room air. However, despite the appropriate antibiotic cover, the patient's condition deteriorated. He was lethargic and had increased regurgitation of feeds, so he was kept nil orally and intravenous fluids (Isolyte-P) were started. The RT output was non-bilious and was replaced by NS+10mEq/L KCl every 6 hours[2]. On examination, he was tachypnoeic, so a chest X-Ray was done, and the patient was kept on oxygen by nasal prongs @2L/min. The chest X-Ray was normal and there were no infiltrates. The ABG persistently showed hypernatremia with normal ion gap metabolic acidosis. Considering hypernatremic dehydration, the patient was given 0.9% NS bolus 20ml/kg over 20 minutes followed by maintenance fluid (D5 N/2 saline with 20mEq/L KCL) at 125%[2].

Keeping in mind the differential diagnosis of proximal RTA, a bicarbonate loading test was done. The fractional excretion of bicarbonate was measured, and a value>15mEq/L confirmed the diagnosis[3]. Thiazide diuretics along with spironolactone in combination with calculated sodium in the fluid decreased the urine output.

The patient was administered 1mEq/kg NaHCO3 for 3 days and a repeat ABG every 12 hours revealed decrease in metabolic acidosis and hypernatremia. The daily dose of sodium bicarbonate was raised to 3mEq/Kg.

This was followed by clinical improvement. The patient's gastric residues decreased and gradually the feeds were started. The patient started accepting RT feeds well and was shifted to oral feeds. Oxygen was gradually weaned off. Intravenous antibiotics were stopped after 14 days. The baby was hemodynamically stable, maintaining saturation on room air, breastfeeding well, and was passing stool and urine, hence was discharged from the hospital with advice to follow up after 2 weeks. He was discharged on oral bicarbonate @5mEq/kg/day.

FOLLOWUP

The child was followed up at 2 weeks, 2 months and 6 months. The repeat ABG at 2 weeks was normal. There was no metabolic acidosis and hypernatremia. The serum bicarbonate was 22mEq/L, so the oral bicarbonate supplementation was continued at 5mEq/kg/day. There was a 2 kg weight gain at 2 months follow-up. The child was breastfeeding well and interacting well with his parents.

III. Conclusion

This case clearly illustrates the importance of early diagnosis and aggressive management for neonatal presenting forms of RTA. All children with proximal RTA require evaluation for associated syndromes like cystinosis, Lowe Syndrome, and Dent disease[3]. The correction of acidosis is prudent by giving exogenous bicarbonate and restriction of dietary sodium. Correction of acidosis results in improved growth velocity.
Since the clinical symptoms mimic sepsis and dehydration, a keen suspicion is required.

Implications for Clinical Practice:
• Undiagnosed cases of RTA can mimic severe sepsis and if undiagnosed can contribute to neonatal morbidity and mortality and financial burden on the parents.
.•With the introduction of sodium bicarbonate, there was a significant clinical improvement, acidosis improved, and on follow-up, there was an improvement in growth velocity.
There was a documented weight gain of 2000gm at the time of discharge.

IV. Discussion

Proximal RTA (type 2) is linked to a reduction in the proximal nephron's capacity to reabsorb bicarbonate[1]. Patients with proximal RTA may present with a wide range of symptoms, from asymptomatic to severe sepsis and shock. Given that the tubular system is still capable of retaining bicarbonate distally, the hyperchloremic metabolic acidosis in proximal RTA is typically less severe. Fanconi's syndrome, which also causes a tubular loss of glucose, calcium, phosphate, and amino acids, is a genetic disorder linked to type 2 RTA[8].

There is a subtype of proximal RTA known as isolated proximal RTA[9]. This condition can be autosomal dominant, autosomal recessive, or sporadic isolated proximal RTA. The RTA is generally a lifelong condition following presentation, regardless of whether it is autosomal dominant or recessive. The sporadic proximal RTA often disappears with therapy[9]. Since recessive types of RTA are frequently characterized by band keratopathy, cataract, glaucoma, and intellectual disability and there is no history of similar complaints in other family members, our case is most likely a presentation of sporadic RTA. There was a clinical improvement after bicarbonate supplementation as well.

Proximal RTA is more commonly a part of a generalized tubular disorder known as Fanconi syndrome which is characterized by global dysfunction of proximal tubules with proteinuria, aminoaciduria, bicarbonaturia, phosphaturia, and glucosuria[10]. However, in our patient, there was no proteinuria and aminoaciduria. There was transient glycosuria during the critical phase of the illness which resolved following bicarbonate supplementation and improvement in the well-being of the neonate.

Hypokalaemia is a common finding in patients with type 2 RTA due to osmotic diuresis as decreased HCO3 reabsorption causes increased flow rate to the distal tubule thereby causing increased K excretion[9,17]. In our patient, there was persistent hypokalaemia which was not responsive to supplementation. Following a week of sodium bicarbonate supplementation, hypokalaemia resolved.

Rare mutations in the gene *SLC*4A4 encoding the sodium bicarbonate cotransporter, are associated with recessive forms of isolated proximal RTA[12]. This disorder presents with severe hypokalemic, hyperchloremic, metabolic acidosis, growth retardation, and ocular abnormalities including glaucoma, cataracts, and band keratopathy[12]. However, our patient did not have the said features on fundus examination. And the whole exon sequencing done later was normal. The etiology of the autosomal dominant form of familial proximal RTA is unclear and is not due to a defect in genes that are known to be involved in proximal bicarbonate reabsorption[5]. Clinical manifestations were limited to short stature and metabolic acidosis as reported in some families. No family history is present in our case.

The neonate presented as a case of severe sepsis and hypernatremic dehydration. The hypernatremia could be due to inherited AD or AR putative mutations in Na-H antiporter in the apical membrane and Na-HCO3 cotransporter in the basolateral membrane of proximal tubular cells respectively[18]. Hypernatremia was also contributed by concurrent nephrogenic diabetes insipidus. Nephrogenic diabetes insipidus has been reported to occur in both proximal and distal RTA due to defective aquaporin 2 channels, hypercalciuria, cystinosis, and as a result of tubulointerstitial nephritis[13,14]. As it lasted just a short time, it is unlikely due to chronic tubular disease and mutations in the transporter, rather more likely due to acute tubular injury sustained from hemodynamic instability, sepsis, and dehydration while he was in the neonatal intensive care unit.

Thiazide diuretics along with spironolactone in combination with calculated sodium in the fluid decreased the urine output. The diuretics by inducing mild volume depletion increase the proximal sodium and water reabsorption, thereby diminishing water delivery to the ADH-sensitive sites in the collecting tubules and reducing the urine output[16].

Bicarbonate infusion test: Fractional bicarbonate excretion is measured after an infusion of bicarbonate. The serum bicarbonate concentration approaches the normal level in the body after the infusion, which is more than the reabsorption threshold of the patient with type 2 RTA. Urine pH rises because of the appearance of greater than 15% of filtered bicarbonate in urine. We also performed the bicarbonate loading test on our patient, and >15% of the bicarbonate was filtered thereby indicating type2 RTA[3,7].

Our patient had hypophosphatemia which resolved after bicarbonate supplementation. Phosphate depletion can be a part of Fanconi syndrome;however the patient did not have amino aciduria. There was also no other evidence of Fanconi's syndrome[5]. Postulated causes for hypophosphatemia are severe hypernatremia and respiratory alkalosis as compensation for metabolic acidosis. This increases intracellular pH leading to increased cellular uptake of phosphate. Besides that, the hypernatremia would cause a negative feedback mechanism resulting in reduced sodium reabsorption in the proximal tubule and therefore phosphate its reabsorption is mediated by a sodium phosphate cotransporter. These hypotheses were reinforced when he no longer required phosphate supplements once the sodium and acid-base disturbances were normalized[16,19].

Hashvina S et al reported a case of newly diagnosed distal RTA complicated with severe hypernatremia and hypophosphatemia admitted to the intensive care unit[16]. However, there is limited literature on hypernatremia and type 2 RTA in a newborn. McSherry E et al in her study investigated the renal acidification defect in four infants with renal tubular acidosis (RTA), including three with classic RTA and one with Fanconi syndrome. She concluded that the fractional excretion of filtered bicarbonate was substantial (6-9%), as well as relatively fixed, over a broad range of plasma bicarbonate concentrations (15-26 mmoles/l)[11]. However, there is limited literature on hypernatremia with type 2 RTA in a newborn, resolving after bicarbonate supplementation.

References

[1]. Mustaqeem R, Arif A. Renal tubular acidosis. InStatPearls [Internet] 2022 Jul 18. StatPearls Publishing.
[2]. Khandelwal P, Bagga A. Fluid, Electrolyte and Acid-base Disorders. Pediatric Nephrology. 2016 May 31:88.
[3]. Sinha A, Bagga A. Tubular disorders. Pediatric Nephrology. 2016 May 31;6:312-16.
[4]. Moshref LH, Moshref RH, Safdar OY. Renal tubular acidosis in pediatrics: A review article. Australasian Medical Journal (Online). 2019;12(2):63-70.
[5]. McSherry E, Sebastian A, Morris RC. Renal tubular acidosis in infants: the several kinds, including bicarbonate-wasting, classic renal tubular acidosis. The Journal of clinical investigation. 1972 Mar 1;51(3):499-514.
[6]. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. The Indian Journal of Pediatrics. 2008 Mar;75(3):261-6.
[7]. Bagga A, Sinha A. Evaluation of renal tubular acidosis. The Indian Journal of Pediatrics. 2007 Jul;74(7):679-86.
[8]. Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. Nephrol Dial Transplant. 2012 Dec;27(12):4273-87. doi: 10.1093/ndt/gfs493. PMID: 23235953; PMCID: PMC3616759.
[9]. Soriano JR. Renal tubular acidosis: the clinical entity. Journal of the American Society of Nephrology. 2002 Aug 1;13(8):2160-70.
[10]. Alper SL. Familial renal tubular acidosis. Journal of nephrology. 2010 Nov 1;23:S57-76.
[11]. McSherry E, Sebastian A, Morris RC. Renal tubular acidosis in infants: the several kinds, including bicarbonate-wasting, classic renal tubular acidosis. The Journal of clinical investigation. 1972 Mar 1;51(3):499-514.
[12]. Demirci FY, Chang MH, Mah TS, Romero MF, Gorin MB. Proximal renal tubular acidosis and ocular pathology: a novel missense mutation in the gene (SLC4A4) for sodium bicarbonate cotransporter protein (NBCe1). Mol Vis. 2006 Apr 10;12(35-36):324-0.
[13]. Wrong OM, Norden AG, Feest TG. Dent's disease; a familial proximal renal tubular syndrome with low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, metabolic bone disease, progressive renal failure and a marked male predominance. QJM: An International Journal of Medicine. 1994 Aug 1;87(8):473-93.
[14]. LOWE C, Terrey M, MacLachlan EA. Organic-aciduria, decreased renal ammonia production, hydrophthalmos, and mental retardation: a clinical entity. AMA American journal of diseases of children. 1952 Feb 1;83(2):164-84.
[15]. Das D, Sinha R, Dey S. Renal Tubular Acidosis Presenting as Nephrogenic Diabetes Insipidus. Indian Pediatrics. 2019 Apr 1;56(4).
[16]. Sukesh H, Zarim MH, Hassan WH. Hypernatremia and Hypophosphatemia in Distal Renal Tubular Acidosis: A Case Report of Acid-base and Electrolyte Misadventure.
[17]. Batlle D, Moorthi KM, Schlueter W, Kurtzman N. Distal renal tubular acidosis and the potassium enigma. InSeminars in nephrology 2006 Nov 1 (Vol. 26, No. 6, pp. 471-478). WB Saunders.
[18]. Ritter M, Fuerst J, Wöll E, Chwatal S, Gschwentner M, Lang F, Deetjen P, Paulmichl M. Na+/H+ exchangers: linking osmotic dysequilibrium to modified cell function. Cellular Physiology and Biochemistry. 2001;11(1):1-8.
[19]. Suzuki S, Egi M, Schneider AG, Bellomo R, Hart GK, Hegarty C. Hypophosphatemia in critically ill patients. Journal of critical care. 2013 Aug 1;28(4):536-e9.

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