CLINICAL VIGNETTE

A Review of Renal Tubular Acidosis and Two Example Cases with Type I and IV Defects

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Introduction

Renal tubular acidosis (RTA) syndromes are defects in renal acid excretion or bicarbonate handling that occur for diverse hormonal and functional etiologies. It is important to distinguish RTA Syndromes from acidosis due to chronic renal failure. By definition renal tubular acidosis occurs with normal, stable or relatively preserved renal function. They produce a non-anion gap acidosis not accounted for by renal failure, or gastrointestinal bicarbonate loss (commonly from naso-gastric tube losses or diarrhea).[1]

The numbering scheme for renal tubular acidosis is quite confusing because numbers were assigned historically in the order of discovery. Type I is distal renal tubular acidosis that was discovered first,[2] followed by type II proximal renal tubular acidosis. Type III was identified with amphotericin use and is a combination of types I and II and omitted from numbering scheme.[3,4] Type IV is a distal renal tubular acidosis due to hypoaldosteronism that results in hyperkalemia, rather than an actual distal acidification defect in the cortical collecting duct.[5] See Figure 1 for a schematic of acidosis types, the cellular defects, that result in each one, and characteristics. We present two cases that demonstrate the different calculations needed to make a diagnosis of a renal tubular acidosis and the clinical correlations associated with each type.

Case Reports

Case 1

A 74-year-old Caucasian female with mild chronic kidney disease, serum creatinine at 1.4-1.5 mg/dL and chronically low serum bicarbonate levels of 11-15meq/L. She presented several times with a worsening anion gap due to infections. Serum anion gap was calculated as [sNa-(sCl+HCO3]. In one instance her sodium was 145 meq/L, potassium was 3.6 meq/L, chloride was 121 meq/L, serum bicarbonate was 15 meq/L, serum anion gap was 9, BUN was 48 (stable from prior values), and serum creatinine was 1.5 mg/dL consistent with above. Of note, the serum albumin was 3.8-3.9 confirming the normal serum anion-gap value as accurate.

Urine studies showed a urine sodium of 84 meq/L, urine potassium of 13.8meq/L, and urine chloride of 98 meq/L. Urine anion gap calculated at uNa+uK-uCl= 0 was borderline and considered positive in some cases. Urine osmolal gap was calculated according to 2*(UNa+K)+ urine glucose/18+ urine urea nitrogen (UUN)/2.8 where UUN was 791mg/dL and urine glucose was <7 (not detected, 0). The urine osmolality calculated was 478 mosm/L and urine osmolality measured was 536 mosm/L 58mosm.

These calculations estimated urinary ammonia excretion of 29 mosm/L, which is quite low, and evidence of a distal process. Urinary osmolal gap of <150mosm/L indicates decreased urinary ammonia excretion. The estimated urinary ammonia concentration is the urine osmolal gap divided by 2. This means that any patient with a urinary ammonia excretion <75meq/L has evidence of a distal process impairing ammoniagenesis.

Urine bicarbonate obtained during bicarbonate loading was <5 meq/L indicating that proximal bicarb loss was not the defect, and obviating the need for a fractional excretion of bicarbonate to rule out distal involvement. The data are congruent with the borderline urine anion gap and the positive urine osmolal gap, which pointed to a type I distal renal tubular acidosis.

Case 2

A 78-year-old Caucasian female who presented with hyperkalemia (K=5.7meq/L), and acidosis, with serum bicarbonate of 16-20meq/L. Serum anion gap ranged between 12-16 (borderline) [Na 134,Cl 98,HCo3 20, AG=16] with a normal serum albumin of 4g /L. Please note that in the UCLA lab a serum anion gap of 16 is still considered within normal limits, but to be sure a lactate level was checked and was normal as patient was on metformin at the time. Serum creatinine was stable between 1.3-1.4 and patient did not have any acute kidney injury. No diarrhea was elicited historically or other causes of gastrointestinal bicarbonate loss.

Urine anion gap was obtained with urine sodium of 46meq/L, urine potassium of 57 meq/L, urine chloride of 85 meq/L= +18 which was positive. Urine osmolal gap was calculated with urine sodium 46 meq/L, urine potassium 57meq/L, urine urea nitrogen 1078 mg/dL, urine glucose not detected. Measured urine osmolality was 696 mosm/L, with urine calculated osmolality = 591 mosm/L. This showed a urine osmolal gap of 105 mosm/L indicating a urine ammonia concentration of 52.5 meq/L. This is lower than the 75meq/L threshold indicating low

urine ammonia excretion. Given the elevated serum potassium of 5.5-5.8, this was diagnostic of type IV RTA.

Discussion

We review the calculations to discern to differenciate types of renal tubular acidosis. Type I is general due to impaired distal acidification, with severe acidosis.[1,2] It is seen congenitally, in nephrocalcinosis, associated with calcium phosphate stones, and with auto antibodies against H+ ATPase in the cortical collecting duct.[2]

Type II RTA has generally mild acidosis. Because distal renal acidification can occur, urine pH can be <5.5. With bicarbonate infusion, uHCO3 and the fractional excretion of bicarbonate increases, raising urine pH > 7 during bicarbonate infusion.[4] Type II renal tubular acidosis is due to proximal tubular dysfunction in bicarbonate reabsorption and handling. Mutations in carbonic anhydrase, bicarbonate channel NHE3, heavy metal poisoning, multiple myeloma, with Fanconi's syndrome and anemia have all been associated with type II. Medications including carbonic anhydrase inhibitors, tompiramate, and tenofivir have also been associated with Type II RTA.[4]

Type IV renal tubular acidosis can occur because of disordered aldosterone signaling, and is generally the only type accompanied by elevated potassium. None of the RTA syndromes occur in setting of acute kidney injury. RTA type IV can accompany mild obstruction and can be responsible for elevated potassium in those syndromes as well. Type IV RTA typically occurs in diabetics as part of a hyporeninemic hypoaldosteronism. Medications including aldosterone antagonists, amiloride, angiotensin converting enzyme inhibitors, aldosterone receptor blockers, and sulfa antibiotics all induce hypoaldosteronism or block downstream mediators of aldosterone.[5] We presented these cases as practical examples of how to detect and determine which type of renal tubular acidosis is present in a given patient.

Figure 1

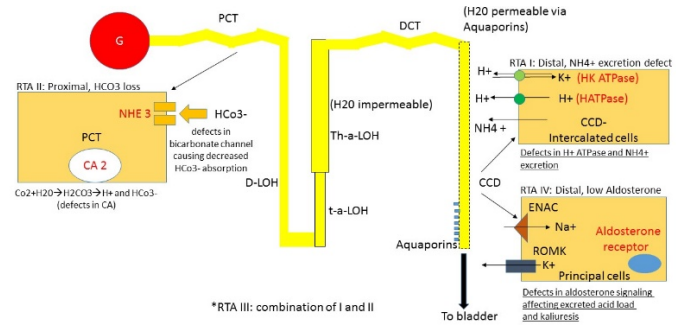

Figure 1: Renal tubular acidosis physiology review
CA2=carbonic anhydrase 2, CCD=cortical collecting duct, CO2= carbon dioxide, DCT=distal convoluted tubule, D-LOH=descending loop of Henle, ENAC=epithelial sodium channel (under aldosterone control),G=glomerulus, H+= proton, H20=water, HCo3=bicarbonate, K+=potassium, NH4+=ammonia, NHE3=bicarbonate channel, PCT=proximal convoluted tubule, RTA=renal tubular acidosis, t-a-LOH=thin ascending loop of Henle, Th-a-LOH=Thick ascending loop of Henle, ROMK=renal outer medullary potassium channel.

Table 1 Renal tubular acidoses characteristics and cases

RTA type	Location	uAG	uOsm gap	physiologic issue	defect	Associations	urine pH	Serum K
RTA I	distal	+	low	decreased uNH4+ excretion	H ATPase	scleroderma	>5.5	low-normal
RTA II	proximal	-	variable	excess uHCO3 loss	CA2, NHE3	MM, Fanconi, CAI	<5.5, >7*	low-normal
RTA IV	distal	+	low	low aldosterone	aldosterone or receptor	DM, sulfa, ACE/ARB	<5.5	high
Case 1-Type I	distal	bl/+	low	decreased uNH4+ excretion	[redacted]	none	6	3.6-4 (L-N)
Case 2-Type IV	distal	+	low	low aldosterone		diabetes	<5.5	5.5-5.8 (H)

Table 1 legend: ACEi/ARB=angiotensin converting enzyme inhibitors/Angiotensin receptor blockers, bl=borderline, CA2=carbonic anhydrase 2, CAI=carbonic anhydrase inhibitors, DM=diabetes mellitus, H=high, K=potassium, L=low, MM=multiple myeloma, N=normal, NHE3= bicarbonate channel 3, RTA=renal tubular acidosis,uAG=urinary anion gap, uHCo3=urinary bicarboante, uNH4+=urinary ammonia, uOsm=urinary osmolal (gap). *=in RTA II alkaline urine can occur during bicarbonate infusion.

Table 1

REFERENCES

1. **Rodríguez-Soriano J, Vallo A.** Renal tubular acidosis. *Pediatr Nephrol.* 1990 May;4(3):268-75. Review. Pub Med PMID: 2205272.
2. **Trepiccione F, Prosperi F, de la Motte LR, Hübner CA, Chambrey R, Eladari D, Capasso G.** New Findings on the Pathogenesis of Distal Renal Tubular Acidosis. *Kidney Dis (Basel).* 2017 Dec;3(3):98-105. doi: 10.1159/000 478781. Epub 2017 Aug 24. Review. PubMed PMID: 29344504; PubMed Central PMCID: PMC5757613.
3. **Yaxley J, Pirrone C.** Review of the Diagnostic Evaluation of Renal Tubular Acidosis. *Ochsner J.* 2016 Winter; 16(4):525-530. Review. PubMed PMID: 27999512; Pub Med Central PMCID: PMC5158160.
4. **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. Review. PubMed PMID: 23235953; PubMed Central PMCID: PMC3616759.
5. **Karet FE.** Mechanisms in hyperkalemic renal tubular acidosis. *J Am Soc Nephrol.* 2009 Feb;20(2):251-4. doi: 10.1681/ASN.2008020166. Epub 2009 Feb 4. Review. PubMed PMID: 19193780.

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