Hypokalemic Distal Renal Tubular Acidosis

Patricia G. Vallés and Daniel Batlle

Distal renal tubular acidosis (DRTA) is defined as hyperchloremic, non-anion gap metabolic acidosis with impaired urinary acid excretion in the presence of a normal or moderately reduced glomerular filtration rate. Failure in urinary acid excretion results from reduced H^+ secretion by intercalated cells in the distal nephron. This results in decreased excretion of NH_4^+ and other acids collectively referred as titratable acids while urine pH is typically above 5.5 in the face of systemic acidosis. The clinical phenotype in patients with DRTA is characterized by stunted growth with bone abnormalities in children as well as nephrocalcinosis and nephrolithiasis that develop as the consequence of hypercalciuria, hypocitraturia, and relatively alkaline urine. Hypokalemia is a striking finding that accounts for muscle weakness and requires continued treatment together with alkali-based therapies. This review will focus on the mechanisms responsible for impaired acid excretion and urinary potassium wastage, the clinical features, and diagnostic approaches of hypokalemic DRTA, both inherited and acquired.

Key Words: Distal RTA, Hyperchloremic metabolic acidosis, Hypokalemia, Growth failure, Acid excretion

INTRODUCTION

The first descriptions of renal tubular acidosis (RTA) were made in children with nephrocalcinosis in 1935 by Lightwood[1] and in 1936 by Butler and colleagues.[2] Later, the term RTA was coined by Pines and Mudge[3] The classical studies of Albright and colleagues[4] characterized the clinical features of the syndrome, documented its association with rickets or osteomalacia, and pointed out to a basic defect in tubular function. This disorder seemed to be relatively rare at first, accompanied with other disturbances of renal tubular transport which were genetically determined in some cases.[5-8] The syndrome, while relatively rare, is of great interest among students of pathophysiology because it was a model of disease in which the biochemical, physiologic, and molecular basis of its pathogenesis could be examined. Unlike adults, in whom RTA is often secondary to acquired causes, children most often have primary forms of RTA. According to their pathophysiological basis, 4 types of RTA were initially categorized.[9-11] Distal type I RTA or classic RTA thereby referred as distal renal tubular acidosis (DRTA) is characterized by reduced net acid excretion and an inability to lower urine pH regardless of the degree of acidemia.[9-14] Proximal type II RTA, by contrast, is characterized by marked HCO_3^- wastage but preserved the ability to lower urine pH when plasma HCO_3^- (and therefore filtered HCO_3^-) is below a certain threshold.[9-11] The term type III RTA was coined to describe patients in whom HCO_3^- wastage coexists with failure to lower urine pH despite profound acidemia.[10-11] The term type IV RTA was introduced by Sebastain and colleagues[12] to designate the type of acidification defect associated with hyperkalemia and attributable primarily to aldosterone deficiency. A hyperkalemic form of DRTA not attributable primarily to aldosterone deficiency was later described.[13-15] This type was also referred to as voltage-dependent RTA to reflect the postulated mechanism that would account for reduced ion secretion, both potassium and hydrogen.[13] This mechanism was postulated based on similarities observed in patients with obstructive uropathy, with the defect observed experimentally in the postobstructed kidney and induced also by the administration of amiloride to block sodium transport.[16,17] As new potential mechanisms were uncovered, the permeability defect theory of DRTA that had been postulated earlier by Seldin and Wilson[18] was no longer tenable as a unique mechanism causing hypokalemic DRTA. Rather, several other potential mechanisms were described.[19-24] Only the alteration in distal acidification caused by amphotericin B, a compound that causes renal potassium wastage and a back leak of protons, demonstrable in epithelial analogs of the mammalian collecting tubule[25-27] has the permeability defect as the mechanism causing DRTA.

Electrolyte disturbances namely hypokalemia or hyperkalemia are key distinctive features of each type of RTA. The clinical phenotype in patients with DRTA associated with hypokalemia is very rich and is characterized by stunted growth with bone abnormalities in children as well as nephrocalcinosis and nephrolithiasis that develop as the consequence of hypercalciuria, hypocitraturia, and relatively alkaline urine. Unique systemic manifestations such as deafness are found in inherited types in which the defect in transporting hydrogen ions is due to mutations in a V-ATPase present in the ear and the kidney collecting tubule. The hyperkalemic forms of RTA, discussed elsewhere in this issue, are usually acquired and lack a specific clinical phenotype other than that of the underlying kidney disease, and alterations in calcium metabolism usually are not present.[13-15,28-29] Advances in renal physiology and the molecular biology of acid-base transporters have allowed a much better understanding of DRTA in general, particularly

From the Pathophysiology Division, Pathology Department, School of Medicine, National University of Cuyo, Mendoza, Argentina; and Division of Nephrology, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Support: Grant support to D.B. from R01DK104785.

Address correspondence to Daniel Batlle, MD, Earle Del Greco Levin endowed Professor of Medicine, and Hypertension Division of Nephrology, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL. E-mail: d-batlle@northwestern.edu

1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2018.05.003

of the hereditary syndromes.[30-47] In this review, we will discuss DRTA, both inherited and acquired, with an emphasis on the pathophysiology of the metabolic acidosis and the development of severe hypokalemia, a striking finding that often brings the patients to medical attention as a result of muscle weakness and paralysis.

Overview of Distal Acidification in DRTA

The site of the nephron responsible for the causation of DRTA is felt to be the late distal convoluted tubule and the collecting tubule. Intercalated cells in these nephron segments are responsible for acid secretion by the α-intercalated cell and bicarbonate secretion by the β-intercalated cell (Fig 1). In α-intercalated cells, urinary acidification involves a combination of energy-dependent proton secretion across the apical surface which is mediated mainly by a hydrogen ATPase and to a lesser extent by a hydrogen potassium ATPase.[48-51] Basolateral chloride-bicarbonate exchange that serves to transport bicarbonate back into the blood occurs via a band-3 protein, AE1, which is also critically important for the process of continued acid excretion via the apical H^+-ATPase and H^+/K^+-ATPase pumps (Fig 1)

DRTA can be attributed to failure of the kidney α-intercalated cells to acidify the urine normally as a result of dysfunction in any of the transporters involved in the overall process of acidifying the urine maximally (Fig 1). In DRTA, urine pH is typically well above 5.5 regardless of the degree of systemic acidosis[9-13,30,31] (Fig 2). As a result of impaired distal H^+ secretion, there is not only a failure to lower urine pH maximally but also, more importantly, the excretion of acid as ammonium and other buffers, collectively referred as titratable acids, is markedly decreased.[30,31,43] Typically, the overall level of kidney function is well preserved, and the glomerular filtration rate is normal or near normal so that the formation of ammonia is not limited by a reduced nephron mass. In fact, the associated hypokalemia should increase ammonia formation in the proximal tubule which perhaps provides some degree of compensation for the metabolic acidosis, but this, to our knowledge, has not been formally evaluated. Even when the urine is alkaline, the amount of bicarbonate in the urine is modest and contributes very little to the overall decrease in net acid excretion in DRTA. The decrease in net acid excretion over time results in the development of a hyperchloremic type of metabolic acidosis, the hallmark of DRTA. Kurtz and colleagues[52] have postulated that the decrease in urine ammonia excretion is associated with increased renal vein ammonia delivery with concomitant HCO_3^- consumption in the urea cycle. This would be in part the consequence of the relatively high pH that prevails in the collecting tubule when proton secretion is diminished.[52]

CLINICAL SUMMARY

- In children, DRTA is most often observed as a primary entity. Growth retardation and bone loss are often present because of chronic metabolic acidosis unless alkaline therapy is initiated early.
- Associated features include nephrocalcinosis, nephrolithiasis, hypercalciuria, and hypocitraturia.
- Patients may suffer from weakness and muscle paralysis due to hypokalemia, a striking feature of DRTA.
- Hearing loss is seen in the autosomal recessive type of DRTA caused by mutations in ATP6V1B1 and ATP6V0A4.

The impaired excretion of both NH_4^+ and titratable acid is generally attributed to the decrease in H^+ secretion by α-intercalated cells in the distal nephron to acidify the urine normally.[33-38] This results from dysfunction in any of the acid-base transporters in the intercalated cell involved in the overall process of acidifying the urine (Fig 1). Enhanced bicarbonate secretion by the β-intercalated cell could theoretically also cause decreased net acid excretion, but no cases of DRTA attributable to this mechanism have been clearly demonstrated to date. This could occur with an abnormal targeting of AE1 to the apical rather than the normal location in the basolateral membrane of the α-intercalated cell (Fig 1).

It should be noted that the rate of H^+ secretion by α-intercalated cells is importantly influenced by the rate of Na^+ transport in the neighboring principal cells that are directly involved in Na^+ reabsorption and K^+ secretion but not in H^+ secretion. In the cortical collecting tubule, principal cells are the predominant type.[49-51] The lumen-negative potential difference usually prevailing in the cortical collecting tubule which is generated by active Na^+ reabsorption favors the secretion of H^+ and K^+ ions.[53-57] Maneuvers that obliterate lumen electronegativity in the cortical collecting tubule (CCT) have been shown to inhibit H^+ and K^+ secretion.[53-57] In contrast, the medullary collecting tubule secretes H^+ independently of Na^+ transport.[57-59] From these observations, we postulated that assessment of acidification by the CCT *in vivo* should be possible using maneuvers that enhance only sodium-dependent acidification.[23] Furosemide and other loop diuretics should provide a tool to assess sodium-dependent acidification by the CCT. We reasoned that this approach should be more practical than the administration of sodium sulfate, a powerful stimulus for sodium-dependent acidification.[23] First, by blocking NaCl reabsorption in the thick ascending Loop of Henle, loop diuretics increase Na^+ delivery to the collecting tubule. Second, by increasing Na^+ reabsorption in the CCT, they should result in the creation of a favorable transtubular voltage (lumen negative) and thus enhancement of H^+ and K^+ secretion. This postulation requires that a stimulatory effect of loop diuretics on CCT acidification and K^+ excretion be totally or partially prevented by amiloride, an agent well known to block Na^+ reabsorption and to thereby inhibit acidification and K^+ secretion in the CCT.[53] Third, furosemide does not exert any direct effect on acidification by the collecting tubule.[60] The notion that loop diuretics increase sodium-dependent