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Renal tubular acidosis: 'RTA is no accident'

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Introduction

The term 'renal tubular acidosis' (RTA) might logically be applied to any form of renal disease causing systemic acidosis, since the renal tubule is the only part of the kidney involved in acid excretion. By convention, however, the term is not used for the acidosis of patients with end-stage renal disease (ESRD), although they are usually acidotic. For patients who are acidotic from predominantly tubular disease, now known as RTA, Fuller Albright[1] originally coined the portmanteau expression 'renal acidosis resulting from tubular-insufficiency-without–glomerular-insufficiency'. Over the 60 years following his pioneering work, a jumble of different diseases have been described that could be covered by this expression. Of these, the most clearly defined and recognisable form, and the one in which the molecular defects responsible have been best elucidated, is the syndrome known today as distal renal tubular acidosis (dRTA); also called 'classical', 'type 1' or 'hypokalaemic' RTA, terms that encapsulate both its origin and one of its cardinal clinical features. This syndrome is characterised functionally by hyperchloraemic (non-anion gap) acidosis and defective urinary acid excretion (with a urine pH that cannot fall below 5.3). Clinically, it is characterised by the presence of rickets (osteomalacia), renal stones or nephrocalcinosis, and as already mentioned, hypokalaemia.

History matters

Distal RTA

The London paediatrician Reginald Lightwood[2] is usually credited with the discovery of this syndrome. In 1935, he described necropsies of six infants who failed to thrive and died aged 5–11 months. Their kidneys showed 'calcium infarction' — macroscopic deposits of calcium — for which Albright later introduced the term 'nephrocalcinosis'. Lightwood's brief report gave no details of renal histology, blood or urine chemistry, and it has been argued that his cases might have included some in which the hypercalcaemia was caused by vitamin D intoxication or idiopathic infantile hypercalcaemia (Williams syndrome), or by even more bizarre causes such as renal tubular damage from the contemporary use of mercury in 'teething' powders. In the following year, however, the Boston group of Butler, Wilson and Farber[3], in their classic paper 'Dehydration and acidosis with calcification at renal tubules', reported that systemic acidosis and failure to excrete a highly acid urine were features of four infants with necropsy findings similar to Lightwood's cases. These children died despite attempts to treat their acidosis with oral and parenteral alkalis. In an appendix, Butler *et al.* described a 10-year-old rachitic boy with a similar syndrome. They also described a similarly affected young man aged 20 who had recently undergone removal of a parathyroid tumour — possibly the first recorded case of dRTA resulting from hypercalcaemic renal damage.

Over the next 15 years, several groups reported the disease in both children and adults, and it became clear that, in addition to acidosis, nephrocalcinosis and renal stones, other important features of RTA were potassium depletion and bone disease in the form of rickets (osteomalacia). Most of these features could be abolished or improved by alkali treatment. In 1951, Pines and Mudge[4] became the first to use the term 'renal tubular acidosis' when they reviewed the cases of 16 patients aged 10–49 with osteomalacia caused by the syndrome. They pointed out that the majority of patients, 12 out of 16, were women.

Meanwhile renal physiologists, led by Robert Pitts[5] and his colleagues at Cornell, were establishing the main features of normal renal acid excretion. In humans, the resting urinary hydrogen ion (H^+) or proton ('acid') concentration averages about 1 µmol/l (equivalent to pH 6.0); under acidotic stress, urine pH falls to a minimal value in the range 4.5–5.3. The main factor that determines total tubular acid secretion in humans is the tubular reabsorption of about 3,500 mmols of bicarbonate (HCO_3^-), equivalent to 'negative acid', filtered by the glomeruli each day. Normal subjects on an average diet excrete around 70 mmols of acid in their urine daily, about 30 mmols of which is H^+ attached to urinary buffers, mainly phosphate, as titratable acid (TA, which is mainly $H_2PO_4^-$). About 40 mmol is secreted as H^+ bound to urinary ammonia (NH_3) as ammonium ion (NH_4^+), the NH_3 of which is synthesised in the proximal tubular cell by deamination of glutamine. Pitts established that in humans urinary ammonium had a reserve capacity of up to 250 mmols daily when subjected to an acid load for several days, but that TA had very little reserve as urine pH fell not less than 4.3 with systemic acidosis. TA excretion, therefore, was limited mainly by the rate of buffer, largely phosphate, excretion. (This is the reason why overzealous dietary phosphate excretion and the use of phosphate binders in chronic renal failure can worsen acidosis by reducing available TA.) Pitts found that urinary bicarbonate was negligible in urines that were more acidic than pH 6.5, but could increase significantly with alkali loading, with commensurate increases in urine pH into the range 7–8. By general agreement, total daily net urinary H^+ or net acid excretion (NAE) has since been defined as TA plus NH_4^+ minus HCO_3^- in mmol/day.

In 1959, Wrong and Davies,[6] who were working in Manchester, published details of acid excretion in a large number of patients

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with various forms of renal disease. They used a small dose of ammonium chloride (NH_4Cl), which was sufficient to lower plasma bicarbonate by 3–4 mmol/l, as an acidotic stimulus. Normal subjects were able to lower their urine pH to below 5.3 (5 µmol H^+/l); most patients with renal failure were equally efficient in lowering their urine pH, but had markedly reduced rates of ammonium excretion, roughly in proportion to their reduced overall renal function as measured by glomerular filtration rate (GFR). Patients with dRTA had minimum urine pH values in the range 5.7–7.0 and their urinary TA excretion was reduced, in keeping with their abnormally raised urine pH. Most strikingly, urinary NH_4^+ excretion rates in these dRTA patients were reduced in proportion to GFR. This suggests that a reduction in renal mass, rather than any specific tubular defect of ammoniagenesis and excretion in dRTA, was responsible for this defect. Support for this conclusion came from three patients who had nephrocalcinosis without systemic acidosis. These patients were unable to lower their urine pH below 5.7–6.5, with commensurate reductions in urinary TA, but had well-preserved GFR and normal or even enhanced rates of urinary NH_4^+ excretion, which appeared to protect them from systemic acidosis. This syndrome variant was described as 'an incomplete form of renal tubular acidosis', that is, a urinary acidification defect similar to that in dRTA but not accompanied by acidosis; it has since been recognised by others. Wrong and colleagues were also the first to demonstrate a reduction in urinary pCO_2 in patients with dRTA.[7]

Proximal RTA

Early work on RTA did not distinguish between the parts of the renal tubule where disease might cause acidosis. It was clear in Albright's monumental work, however, that some patients had clinical features of proximal tubular disease, including the glycosuria, phosphaturia, aminoaciduria and low-molecular-weight proteinuria of the so-called renal Fanconi syndrome, whereas others lacked these features and usually had nephrocalcinosis. By 1970, these two groups of patients were being described as having either 'proximal' or 'distal' RTA, also designated as types 2 and 1, respectively. Later, the label 'type 3' was attached by Curtis Morris[8] and his group in San Francisco to the rare paediatric cases that had features intermediate between types 1 and type 2. (Their disease was most likely the result of a defect in carbonic anhydrase-II, which is present in both proximal and distal tubular cells that have the capacity to secrete H^+.) The term 'type 4' was applied to cases of distal tubular disease in which mineralocorticoid deficiency or resistance led to hyperkalaemia and acidosis. These cases are best described as 'hyperkalaemic dRTA', a term that was sometimes used to refer to the form of distal RTA here designated as 'type 1' (see Table 1). Although most patients with the newly described 'proximal' or type 2 RTA had features of a generalised proximal tubular deficit, some patients with isolated defects of proximal bicarbonate reabsorption were discovered. These included patients with a sporadic and transitory form that affects infants and young children, and those with a rare recessive familial form caused by mutations affecting the electrogenic Na^+–bicarbonate co-transporter, which is associated with various ocular defects.[9] Over the years, it has become clear that proximal RTA in all its forms is much less common than the many forms of distal RTA, so inevitably it has been less studied. By contrast, more and more causes of dRTA have been reported, including renal transplantation, hypercalcaemic and obstructive renal damage, toluene or glue sniffing, chronic lithium administration, amiloride, use of the artificial sweetener cyclamate, use of the fungal antibiotic amphotericin B, and fetal-alcohol syndrome. The number of reports in these categories has been small, many consisting of single case reports, so it has been difficult to establish the underlying molecular basis of the urinary acidification defect. Two forms of dRTA have, however, turned out to be relatively common: 1) the form associated with systemic autoimmune diseases, affecting predominantly adult females; and 2) various inherited forms of dRTA, both autosomal dominant and recessive. The sheer number of cases of these two forms of dRTA has encouraged an intensive study of the molecular basis of their disease, details of which are discussed briefly below.

Table 1: Classification of renal tubular acidosis (RTA)

Type 1 or **distal RTA** with hypokalaemia – forms are described as 'complete' or 'incomplete' depending on whether the plasma bicarbonate concentration is less than or more than 20 mmol/l, respectively.

Type 2 or **proximal RTA** is rarely isolated, but it is usually part of a renal Fanconi syndrome.

Type 3 RTA was originally described in infants as an 'immature tubule', but is now used to describe a mixture of types 1 and 2; the best example being carbonic anhydrase deficiency or inhibition.

Type 4 RTA is 'distal-like' and results from a real or apparent lack of aldosterone. Unlike those with type 1 distal RTA, type 4 patients are usually hyperkalaemic and have reduced ammoniagenesis.

During the 1950s, several groups used intravenous infusions of buffered phosphate to study TA excretion. The patients studied included people with all forms of dRTA, including adults, infants and patients with familial disease. Invariably, urinary TA excretion rates increased in proportion to the increase in urinary phosphate excretion rate, although urine pH did not fall below the abnormal level already recorded. Thus, tubular secretion of H^+ in dRTA appeared not to be rate-limited but rather gradient-limited, in that it could not occur against a urinary pH gradient that was greater than approximately 100:1 (the concentration difference between plasma pH at 7.40 and normal minimum pH of about 5.40).

From 1975 to 1986

In the late 70s and 80s, a group of nephrologists in Chicago made detailed physiological studies of the tubular defects responsible for dRTA, mainly using animal models. Their studies

examined the effects of lithium toxicity, toluene and amphotericin B exposure, urinary obstruction, rejecting renal transplants, mineralocorticoids and various diuretics.[10] These workers contributed greatly to our knowledge of how these factors (all rather unusual as causes of clinical dRTA) might influence urinary composition, but they made few observations on the human disease (simply labelled as 'idiopathic dRTA'). They did not distinguish between the various forms and different causes of clinical dRTA that were increasingly being recognised by clinical nephrologists. Of interest is their 1980 remark that, as a cause of dRTA 'a defect in the exit step for bicarbonate at the serosal membrane' (of the tubule) is currently without precedent; the expression of such a defect is difficult to predict on the basis of currently available information'.[10] In fact, as described below, this defect has since been found to be the most common cause of inherited dRTA.

From 1997 to present

Later and more recent studies have emphasised the large number of abnormal conditions that might cause a secondary form of clinical dRTA, including any cause of hypercalcaemia or nephrocalcinosis, medullary sponge kidney (MSK), sickle-cell disease, and various forms of chronic tubule-interstitial nephritis. In most nephrology units, however, secondary dRTA from these various causes is less common than dRTA in which a primary cause can be found. Among these primary cases are two distinct forms of clinical dRTA whose study has been particularly rewarding: 1) familial dRTA, although not particularly common, offers the possibility of identifying a precise genetic cause of the disease; and 2) 'autoimmune' dRTA, a form of the disease that affects mainly mature women. 'Autoimmune' dRTA is characterised by numerous circulating autoantibodies that are directed particularly at non-renal organs. It is now emerging as the most common form of dRTA seen in the West, and is likely to be caused by precise and identifiable forms of autoimmune injury that affect the mechanisms of distal H^+ secretion.[11]

The familial forms of RTA, excluding the rare proximal form referred to earlier, cause dRTA and involve the two main molecular players in H^+ secretion along the collecting duct, the apical proton secreting H^+-ATPase electrogenic pump and the basolateral bicarbonate secreting Cl^-/HCO_3^- exchanger.[12] The latter is a truncated form of the same exchanger present in red blood cells, which is essential for normal CO_2 transport and transfer. Mutations in these two transporters are responsible for all cases of familial dRTA described to date. Mutations of the H^+-ATPase cause a recessive and more commonly paediatric form of dRTA with early- or late-onset deafness occurring because this pump is also present in the inner ear. Mutations of the Cl^-/HCO_3^- exchanger cause a dominant form of dRTA that is usually picked up later in life, particularly in patients with nephrocalcinosis and renal stones. Red blood cell abnormalities are not a feature of this form in Caucasians, but this is not the case in tropical populations where it can also be recessive.[12] In adult nephrology, familial and *de novo* autosomal dominant dRTA and autoimmune dRTA are more likely to be encountered and should be considered as a possibility for any patient with nephrocalcinosis and stones[12]. In autoimmune dRTA, hypokalaemia is often striking and symptomatic, whereas nephrocalcinosis can be less prominent. MSK, a diagnosis that can be made confidently only with an intravenous urogram, can also be familial and might be confused with autosomal dominant dRTA, although both can occur as isolated forms of disease.

Summary

RTA is a generic term that is used to describe several disorders in which there is a failure of normal renal acid excretion. Acid retention as a result of impaired renal function occurs in ESRD. In this setting, however, the problem is a reduction in nephron number and reduced urinary buffer excretion, rather than a defect in renal tubular function and H^+ secretion. In RTA, there is usually a hyperchloraemic normal anion gap acidosis (whereas ESRD is associated with an increased anion gap) and generally a preserved GFR. Ammonium excretion can be reduced, but this probably reflects reduced conversion of NH_3 to NH_4^+ because of impaired H^+ secretion, rather than a decrease in ammoniagenesis. RTA can be divided broadly into proximal and distal types. These structural and pathophysiological classifications correspond to the functions of the proximal tubule in reclaiming filtered bicarbonate and generating bicarbonate as a by-product of ammoniagenesis from glutamine, and of the distal tubule and collecting duct in determining net acid excretion.

Proximal RTA (type 2) is usually part of a renal Fanconi syndrome and this is associated with characteristic low-molecular-weight proteinuria. A characteristic feature of distal RTA (type 1), the more commonly encountered adult form of RTA, is a low urinary citrate concentration and excretion rates. Measuring urine pH alone is insufficient to confirm a diagnosis of RTA, unless the pH is >5.3 with systemic acidosis and a near normal GFR (without urinary infection). The best confirmatory test is a

Table 2: Diagnosis of renal tubular acidosis (RTA)

- In the presence of systemic acidosis (see Table 1) and urine pH >5.3
- A casual early morning (second void) urine can be suggestive if urine pH >5.5 and urine citrate/creatinine ratio is low (in an alkaline urine)

Tests for urinary acidification:

- The oral NH_4Cl (0.1 g/kg) test
- The oral furosemide (40 mg) plus fludrocortisone (1 mg) test
- Intravenous bicarbonate loading in suspected proximal RTA to demonstrate a fractional bicarbonate excretion of >15%

Less reliable or indirect tests of urinary acidification:

- Urine-blood pCO_2 difference <30 mmHg (4 kpa) considered abnormal
- Urine anion gap or net charge (negative when acidotic) or osmolar gap (positive when acidotic) are surrogates for unmeasured ammonium ion excretion

urinary acidification test using oral NH_4Cl, or furosemide with fludrocortisone, which should cause urine pH to fall below 5.3. In proximal RTA, if the plasma bicarbonate concentration is low and the filtered bicarbonate load is reduced, urine pH can fall to <5.3, but this is not the case in distal RTA. An approach to the diagnosis of RTA is summarised in Table 2.

Treatment of RTA is mainly with oral alkali, given as potassium citrate or bicarbonate, especially if hypokalaemia is present. In hyperkalaemic distal RTA (type 4), the underlying mineralocorticoid defect is treated. Correcting the acidosis in RTA has more to do with maintaining growth in children and protecting bones in adults, and has only a modest effect on the progression of nephrocalcinosis or renal stone disease. The recent genetic advances in, and insights into, RTA have not yet translated into any new therapies. They have, however, improved our understanding of renal acid-base transport mechanisms and highlighted the wider prevalence of RTA and its complications, thereby promoting its earlier recognition and treatment.

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