CASE REPORT

Alport's syndrome with type 4 renal tubular acidosis

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SUMMARY

This case report details a 51-year-old man with Alport's syndrome resulting in chronic nephritis with stable renal function and sensorineural deafness. The patient was being investigated for persistently raised potassium refractory to dietary and pharmacological modification. Subsequently, the patient was found to have type 4 renal tubular acidosis, and potassium normalised with the addition of fludrocortisone.

BACKGROUND

The association between type 4 renal tubular acidosis (RTA 4) and Alport's syndrome is extremely rare with a PubMed search only highlighting one other documented case in 1993. This case report not only documents the rare association between these two conditions but also highlights the importance of diagnosing the underlying cause of raised potassium. Due to the uncommon association between the two conditions, the diagnosis and treatment of RTA 4 was delayed for a significant period. Importantly, the patient's potassium was not controlled until treatment was initiated. We provide a refresher in the causes of hyperkalaemia and RTA 4 while also adding to the evidence that Alport's syndrome and RTA 4 can occur concomitantly.

CASE PRESENTATION

This case report describes a 51-year-old man with progressive sensorineural hearing loss, chronic nephritis, proteinuria and haematuria. At age 35 years, he was diagnosed with Alport's syndrome following a renal biopsy, and over the subsequent years, renal function remained stable. Throughout the years of 2010–2013, the patient had a refractory hyperkalaemia (see [table 1](#)) in addition to low blood bicarbonate and a low urinary pH (while on sodium bicarbonate). Ramipril 10mg OD was stopped in March 2010 (no other hyperkalaemic medications were being taken by the patient), and a low potassium diet was followed. In May 2013, the patient was hospitalised due to hyperkalaemia (K+6.6) with a metabolic acidosis. Inpatient aldosterone and renin were measured and consistent with hyporeninaemic hypoaldosteronism RTA 4. He was subsequently treated with fludrocortisone 100 µg OD which promptly corrected his potassium levels which have subsequently stabilised. After the addition of fludrocortisone, the patient's blood pressure was controlled with doxazosin.

INVESTIGATIONS

A renal biopsy was performed in 1997 and demonstrated 11 glomeruli, 2 globally sclerosed and 1

segmental sclerosis, mild focal interstitial fibrosis and tubular atrophy. Immunofluorescence illustrated the absence of immune deposition. Electron microscopy depicted focal marked thinning of the glomerular basement membrane down to 152nm and a mean thickness of 216nm in the range of borderline thinning.

Aldosterone standing was 103 pmol/L (140–850); and lying aldosterone, <70 pmol/L (80–300). Renin standing was 0.2 ng (1.5–5.7); and lying, 0.2 ng (0.2–2.8) (fully suppressed). Serum cortisol was 296 nmol/L (171–536). Twenty-four-hour urine creatinine was 10.1 mmol (9–17); and cortisol, 18 mmol (0–165). Urinary pH was 5 on two occasions in 2011 and 6 in 2013.

At diagnosis, proteinuria was 0.1 g/24 hours; this remained stable, never exceeding 0.14 g/24 hours. Once ramipril was stopped, there was no worsening of proteinuria.

Clinic blood pressure readings were as follows: <140/100 prior to ramipril stopping, 149/115 to 152/116 once ramipril was stopped. With the addition of fludrocortisone, blood pressure was controlled with doxazosin; mean average clinic reading was 132/86.

In the ultrasound of the kidney, the right kidney measured 9.9 cm and was mildly hydronephrotic. The left kidney measured approximately 9.0 cm and appeared to have a slightly reduced cortical depth (6 mm).

OUTCOME AND FOLLOW-UP

Since being started on fludrocortisone, the patient's potassium and bicarbonate have normalised and remained stable (see [table 1](#) and [figure 1](#)).

DISCUSSION**Alport's syndrome**

Alport's syndrome is a hereditary nephropathy resulting from the mutations in genes encoding for alpha-3, alpha-4 and alpha-5 chains of type 4 collagen. The pattern of inheritance is predominantly X linked (80%); the remaining being autosomal recessive (15%) and dominant (5%). The abnormal type 4 collagen chains in the basement membrane of the glomerulus, cochlear and eye lead to progressive renal dysfunction with haematuria and proteinuria, sensorineural deafness and ocular abnormalities.^{1–3}

ACE inhibitors (ACEis) are ubiquitously used in Alport's syndrome by nephrologists and paediatric nephrologists alike for their renoprotective and antiproteinuric effects.^{4,5} In this case, the ACEi was discontinued due to hyperkalaemia. However, only a small amount of proteinuria was present from

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Table 1 : Biochemistry Results

Date	Potassium	eGFR	Bicarbonate
November 2010	5.6	33.1	23
March 2011	5.3	37.3	24
May 2011	5.7	33.4	24
August 2011	5.5	35.7	21
December 2011	5.7	35.7	25
January 2013	6.4	32.9	21
Feb 2013	6.5	34.9	21
June 2013	6.0	32.0	19
Fludrocortisone started			
July 2013	5.4	28.0	19
September 2013	5.7	33.0	21
November 2013	6.0	30.0	21
January 2014	5.1	30.0	24
November 2014	5.0		
December 2014	5.7	27.0	23
May 2015	5.0		
June 2015	4.4	32.0	27
August 2015	4.2	27.0	26
October 2015	4.4	35.0	27

eGFR, estimated glomerular filtration rate.

diagnosis, and the suspension of ramipril has not appeared to increase this (see Results).

Type 4 renal tubular acidosis

RTA are a group of disorders in which metabolic acidosis develops due to defects in the ability of the renal tubules to maintain acid-base balance. These abnormalities can affect either the proximal (RTA 2) or distal (RTA 1 and 4) renal tubules.⁶ RTA 4 occurs when alpha intercalated cells in the distal tubule fail to excrete H^+ ions leading to impaired ammonia generation and reduced NH_4^+ excretion. RTA 4 typically arises as a secondary event (see table 2); this can be drug induced or due to aldosterone deficiency. Medications such as non-steroidal anti-inflammatory drugs, ACEis, trimethoprim, heparin and spironolactone can produce

Table 2 Causes of hyperkalaemic distal (type 4) renal tubular acidosis

Defect	Causes
Mineralocorticoid deficiency	Diabetes mellitus Drugs: NSAIDs; cyclosporine A; β -blockers
Low renin, low aldosterone	
High renin, low aldosterone	Adrenal destruction Congenital enzyme defects Drugs: ACE, ARBs, heparin, ketoconazole
Abnormal cortical collecting duct	Absent or defective mineralocorticoid receptor Drugs: spironolactone, triamterene, amiloride, trimethoprim, pentamidine Chronic tubulointerstitial disease: chronic urinary tract obstruction, sickle cell nephropathy, systemic lupus

ARB, angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug.

Source: Modified from Johnson et al.¹²

RTA 4 by reducing aldosterone production. Diabetic nephropathy and chronic interstitial nephritis can result in the loss of the juxtaglomerular apparatus resulting in hyporeninaemic hypoaldosteronism. A primary disorder of the adrenal gland and renal tubular resistance to aldosterone creates a state of absolute and relative hypoaldosteronism, respectively. Aldosterone promotes hydrogen ion secretion by the intercalated cells and potassium ion secretion by the principal cells. Aldosterone deficiency will therefore result in hyperkalaemic hyperchloremic acidosis, and the resulting hyperkalaemia impairs renal ammonia synthesis.^{7 8}

HYPERKALAEMIA

Table 3 details the numerous causes of hyperkalaemia, which can be organised into impaired renal excretion or extracellular shift of potassium. When considering renal causes, once drug-induced hyperkalaemia has been excluded, the primary consideration for the physician should be impaired renal excretion of potassium. For potassium to be effectively excreted, adequate renal perfusion, functioning renal tubules and normal aldosterone levels are needed—a failure in either of these mechanisms may result in

Figure 1 Graphical representation of potassium levels, pre- and post-treatment with fludrocortisone between November 2010 and May 2016. Red vertical bar represents when treatment was initiated.

Table 3 : Causes of Hyperkalemia

Impaired renal excretion of potassium		Shift of potassium into the extracellular space	
Mineralocorticoid deficiency	Other	Tissue damage	Other
Acquired hyporeninaemic hypoaldosteronism	Renal failure	Rhabdomyolysis	Acidosis
Addison's disease	Systemic lupus erythematosus	Burns	Low insulin levels
Congenital adrenal hyperplasia (recessive or autosomal dominant)	Pseudohypoaldosteronism	Tumour lysis syndrome	Familial hyperkalaemic periodic paralysis
Primary hypoaldosteronism or hyporeninaemia	Drugs	Trauma	Drugs
RTA 4			

Source: Modified from Hollander et al.⁹

hyperkalaemia. Hyporeninaemic hypoaldosterone states should be strongly considered if there is only mild renal impairment or in the presence of diabetic nephropathy.⁹ In our index case, hyperkalaemia persisted after review and modification of medications and diet with only mildly impaired and stable renal function. There was acidic urine and fully suppressed renin and aldosterone levels (hyporeninaemic hypoaldosteronism). It is worth noting that renin is raised in Addison's disease.¹⁰ Finally, his hyperkalaemia only responded to fludrocortisone therapy (see figure 1).

RTA 4 is a well-documented cause of hyperkalaemia and should be considered among the differential diagnosis. Only one case of RTA 4 associated with Alport's syndrome has been described in 1993 in a 38-year-old man with Alport's syndrome who presented with life-threatening hyperkalaemia and required urgent haemodialysis. Subsequent investigations revealed a RTA 4.¹¹

This case highlights the need for a more extensive investigation of refractory hyperkalaemia especially when associated with metabolic acidosis in a patient with mildly impaired renal function and not to merely attribute it to chronic kidney disease.

Learning points

- ▶ Although rare, RTA 4 and Alport's syndrome can occur together.
- ▶ It is important to always look for the underlying pathology in hyperkalaemia and not to merely attribute it to chronic kidney disease, diet or medications.
- ▶ Clinicians should consider the diagnosis of RTA in a patient with refractory hyperkalaemia and metabolic acidosis.
- ▶ Only when the diagnosis was established was this patient's potassium controlled.

This case also shows that although the occurrence of RTA 4 in patients with Alport's syndrome is rare, it should be considered in patients with Alport's syndrome presenting with hyperkalaemia and metabolic acidosis.

Contributors TMD undertook literature search, data collection and writing up of the case and obtained patient consent. CW highlighted the case and oversaw the case report. CC reviewed and edited the case report.

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