DOI: 10.7860/JCDR/2022/56154.16979

Case Report

Internal Medicine Section

Hypokalaemia in Type-4 Renal Tubular Acidosis: A Rare Presentation

SHANJITHA HUSSAIN[1], T SARAVANAN[2], S NIRMALA[3]

ABSTRACT

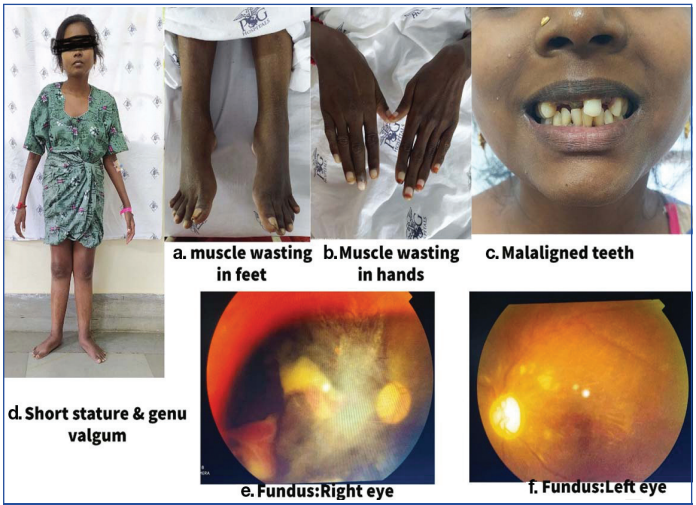
Proximal/Type-2 Renal Tubular Acidosis (RTA) occurs due to impairment of bicarbonate absorption in the proximal tubule and is mainly characterised by hypokalaemia and metabolic acidosis. There are various causes of proximal RTA like genetic, cystinosis, Wilson's disease, drugs and toxins, vitamin D deficiency, hyperparathyroidism, amyloidosis. Vitamin D deficiency is one of the uncommon causes and is more common in elderly. Hereby, authors present a case report of a diabetic and hypothyroid 30-year-old female, who presented with chronic limb weakness, myalgia and bilateral leg swelling. After detailed history taking, clinical examination and laboratory investigations, she was diagnosed with nephrotic syndrome and proximal RTA associated with vitamin D deficiency. She had hypokalaemia with acidosis initially and was managed with diuretics, Angiotensin Converting Enzyme (ACE) inhibitors, vitamin D and potassium supplementation, after which, she developed hyperkalaemia with acidosis. She was evaluated for hyperkalaemic RTA and its common causes and was diagnosed with hyperkalaemic RTA associated with diabetes. Thus, treatment of type-2 RTA due to vitamin D deficiency, led to unmasking of underlying type-4 RTA due to diabetic nephropathy.

Keywords: Angiotensin converting enzyme inhibitors, Diabetes mellitus, Vitamin D deficiency

CASE REPORT

A 30-year-old female presented with complaints of generalised myalgia and muscle cramps, bilateral Upper Limb (UL) and Lower Limb (LL) weakness for the past one year. She had history of dyspnoea on exertion and dysphagia over the past three months. She was known to have type-2 diabetes mellitus, and was on insulin. She was also on thyroid supplements. She had no history of intake of any Over The Counter (OTC) medications. She had history of bilateral leg swelling and facial puffiness over the past two years which was diagnosed elsewhere as nephrotic syndrome secondary to diabetes. But, she had stopped taking the medications soon after.

On examination, she a had short stature and genu valgum, was malnourished and anaemic, with bilateral pitting pedal oedema, UL:LL ratio of 0.8. Oral cavity showed dental caries and malaligned teeth [Table/Fig-1]. Her height was 134 cm, weight was 30 kg, and blood pressure was 110/70 mmHg. Neurological examination showed wasting of proximal muscles more than distal muscles in both UL and LL, power of three in proximal and distal UL muscles on both sides and a power of two in proximal and three in distal LL muscle in both sides and a waddling gait.



[Table/Fig-1]: Clinical findings (a-d), e and f: Fundus examination of both eyes showing bilateral proliferative diabetic retinopathy with right retinal detachment.

On palpation, she had bony tenderness over the lateral chest wall bilaterally. Fundus examination showed bilateral proliferative diabetic retinopathy with tractional retinal detachment in right eye [Table/Fig-1]. Systemic examination of her cardiovascular, respiratory and gastrointestinal systems were normal.

Her initial investigations showed elevated creatinine (1.45 mg/dL) with estimated Glomerular Filtration Rate (eGFR) of 48 mL/min/1.73 m^2. Serum electrolyte showed hypokalaemia, hypocalacemia (Ionised. calcium-0.739; normal range: 1.1-1.3 mmol/L) and metabolic acidosis with normal anion gap. Sodium was 138 mEq/L (normal range: 136-146 mEq/L) [Table/Fig-2].

Parameters	Day 1	Day 3	Day 7	Day 12	Day 16	Day 26	After four weeks follow-up	Reference range (RR)
Urea (mg/dL)	37	50	82				35	14-40
Creatinine (mg/dL)	1.45	1.43	1.70			1.45	1.36 mg/dL	0.66-1.09
Sodium (mEq/L)	138	130	129	134	139	137	141	136-146
Potassium (mEq/L)	3.02	5.6	7.40	6.53	4.7	3.52	4.00	3.5-5.0
Ionised calcium (mmol/L)	0.739	0.945	1.074	0.810	0.789	0.64	0.957	1.1-1.3
Bicarbonate (mEq/L)	16.1	18.3	12.1	7.7	15.8	21.1	19.5	22-30

[Table/Fig-2]: Renal function tests of the patient throughout the course of hospital stay.

Urine Protein Creatinine Ratio (PCR) was in nephrotic range (Urine-PCR:27.16). Her Vitamin D levels were low, Parathyroid Hormone (PTH) was elevated, Alkaline Phosphatase (ALP) was elevated, Total serum calcium was low and serum phosphorus was decreased [Table/Fig-3]. Ultrasonogram (USG) of abdomen showed calcified pancreas with normal-sized kidneys.

The initial clinical impression was diabetic-nephropathy and metabolic bone disease with vitamin D deficiency. She was treated with oral calcium 500 mg BD and vitamin D 1000 IU BD, and started on loop

diuretics, tab. furosemide 20 mg BD and angiotensin converting enzyme Inhibitor (ACEI), tab. enalapril 10 mg OD.

Laboratory investigation	Value (normal range)
Vitamin D (ng/mL)	8 (20-40)
Parathyroid Hormone (PTH) (pg/mL)	226.7 (10-65)
Alkaline Phosphatase (ALP) (IU/L)	405 (20-140)
Total serum calcium (mg/dL)	5.87 (8.6-10.3)
Serum phosphorus (mg/dL)	2.94 (3.5-4.5)

[Table/Fig-3]: Salient laboratory investigations (patient report and the normal range within parenthesis).

After three days of treatment her electrolytes showed severe hyperkalaemia and Normal Anion Gap Metabolic Acidosis (NAGMA). ACEIs were stopped. Treatment was initiated with intravenous insulin in dextrose soultion Q8Hourly, Salbutamol nebulisation 2.5 mg every six hours and oral potassium-binders 15 gm/sachet twice/day and the potassium values, remained persistently elevated. Urinary work-up for RTA was done and reports were suggestive of type-4-RTA as shown in [Table/Fig-4].

Laboratory investigation	Value (normal range)
Urine pH	5.5 (4.6 to 8.0)
Urine sodium (mEq/L)	95.87 (20)
Urine potassium (mEq/L)	12.10 (20)
Urine chloride (mEq/L)	98 (98-106)
Urine protein (mg/dL)	355.5 (0-14)
Urine glucose	2+
Urine Anion Gap (UAG)	Positive
Transtubular Potassium Gradient (TTKG)	2
Serum cortisol (8am) (µ/dL)	5.99 (5-25)
Creatine phosphokinase (U/L)	172 (26-19)
Serum lactate (mmol/L)	1 (0.5-1)
Autoimmune profile (ANA profile, ANA IF, ANCA profile, Rheumatoid factor)	Negative
Viral serology (HIV, Hepatitis B and C)	Negative
Serum electrophoresis	Negative for myeloma

[Table/Fig-4]: Work-up for RTA.

Slit lamp examination for cystine corneal deposits was normal. Fasting (8 am) serum cortisol for Addison's disease was normal. Normal Creatine-phosphokinase (CPK) ruled out any muscle injury. Normal lactate levels reduced the possibility of presence of mitochondrial dysfunction. Autoimmune profile, viral serology, Serum-electrophoresis were negative. USG-abdomen ruled out obstructive uropathy. Renal biopsy reports showed diabetic glomerulosclerosis.

She was treated with tab. fludrocortisone 0.1 mg as OD and bicarbonate infusion for three days, then switched to oral route following which potassium (3.52 mEq/L) and bicarbonate (21.1 mEq/L) levels normalised on day 26 of hospital stay. On day 25 her weakness which, as assessed neurologically, improved with a power of 4/5, and the oedema also reduced clinically.

She was discharged with oral fludrocortisone 0.1 mg OD, vitamin D 1000 IU and calcium 500 mg BD. After four weeks of follow-up her potassium was in normal range and creatinine was 1.36 mg/dL.

DISCUSSION

The RTA is a group of disorders that occurs as a result of disruption to the acid base homeostasis mechanisms. On clinical and patho-physiological basis, RTA are classified into three main categories: i) Proximal/type-2-RTA ii) Distal/type-1-RTA and iii) Hyperkalaemic/type-4-RTA [1]. Proximal/type-2-RTA is caused by impairment in proximal reabsorption of bicarbonate ions. It can occur as an isolated defect or in association with other proximal tubular defects (Fanconi syndrome). It can be either hereditary or secondary to various diseases. Stunted growth is the most common presentation in children. Osteopenia and pseudofractures are seen in adults. Common causes of proximal RTA are cystinosis, Fanconi syndrome, multiple myeloma, primary hyperparathyroidism, Sjögren's syndrome, antiretroviral drugs and chemotherapy drugs, Wilson's disease, vitamin D deficiency [1,2].

The type-4-RTA, is caused due to aldosterone deficiency/resistance or by its inhibition by drugs. It presents as hyperkalaemic-hyperchloraemic metabolic acidosis. Hyperkalaemia impairs renal ammonia synthesis. Common causes include Addison's disease, diabetic nephropathy, Acquired Immunodeficiency Syndrome (AIDS) nephropathy obstructive-uropathy, Lupus nephritis, Amyloidosis, analgesic abuse nephropathy, drugs like Cyclooxygenase (COX) inhibitors, ACEI, Heparin and potassium-sparing diuretics [3]. Hyporeninemic-hypoaldosteronism is the most common cause of Type-4-RTA. Correction of hyperkalaemia and alkali therapy corrects and maintains acid-base equilibrium. Mineralocorticoid replacement is effective [4]. Type-2-RTA, commonly presenting in children in form of rickets in the context of Fanconi syndrome is due to genetic cause. In adults type-2-RTA in context of Fanconi syndrome, as seen in index patient, was mostly due to an acquired cause [5,6]. The common presentation is stunted growth, muscle weakness [5], with osteomalacia and bony deformity with pain being observed in patients with concominant vitamin D deficiency [7,8]. The index patient had limb weakness, muscle cramps and wasting, bone pain, short stature, genu valgum with fluid retention.

Laboratory investigations of type-2-RTA with Fanconi syndrome usually shows hypokalaemia, metabolic acidosis, hypocalacemia, hypophosphataemia, glycosuria, nephrotic proteinuria [7,8]. The index patient had hypokalaemia, NAGMA, hypocalacemia, hypophosphatemia, glycosuria, aminoaciduria suggesting a proximal tubular defect. Furthur evaluation showed vitamin D deficiency. Vitamin D deficiency causes low calcium and phosphorus with elevated ALP and PTH which leads to reduced HCO_3 reabsorption in proximal tubule. The increased delivery of HCO_3 to distal tubules increases urine flow rate leading to potassium wasting and hypokalaemia [9]. Other causes of type-2-RTA were ruled out. The age of onset, absence of extra-renal manifestations of genetic causes and negative history of drug/toxin exposure ruled out other causes of Fanconi syndrome. Other similar cases of vitamin D deficiency causing Fanconi syndrome are reported in literature [7,8].

The patient was treated with potassium, vitamin D and calcium supplementation. She was started on ACEI and loop diuretics. On third day of treatment, she developed severe hyperkalaemia. Arterial Blood Gases (ABG) showed NAGMA. ACEI was stopped. She was treated with anti-hyperkalaemic measures and alkali replacement. Her potassium remained elevated. Type-4-RTA mostly presents with biochemical changes and clinical manifestations could be of the underlying cause for RTA [10,11]. Her urine analysis reports showed a positive UAG which denotes a distal renal defect, urinary pH of 5.5 (acidic) and a TTKG of 2 which denotes that the collecting ducts are not responding to the prevailing hyperkalaemia with an impaired potassium secretion due to either aldosterone deficiency/resistance. These findings were suggestive of type-4-RTA [11]. Diabetic nephropathy leads to renal tubular damage with decreases renin synthesis, therefore aldosterone production, which inturn cause chronic hyperkalaemia [12]. The patient, a diabetic with biopsy proven diabetic glomerulosclerosis, have hyporeninemic-hypoaldosteronism which is the cause of underlying type-4-RTA [10,13]. On treatment with mineralocorticoid and alkali therapy, the refractory hyperkalaemia started responding [4,12]. Characteristics of the types of RTA mentioned in [Table/Fig-5] [1].

Proximal RTA (Type-2)		DISTAL RTA (Type-1)			Hyperkalaemic RTA (Type-4)
		Classic	With HCO_3 wasting (Type-3)	Hypokalaemic	
In situation of metabolic acidosis (Spontaneously or after acid loading)					
Plasma K+	N or D	N or D	N or D	I	I
Urinary anion gap	Negative	Positive	Positive	Positive	Positive
Urine pH	<5.5	>5.5	>5.5	>5.5	<5.5
NH4+ excretion	N	D	D	D	D
Fractional K+ excretion	N or I	I	I	D	D
Ca excretion	N	I	I	I	N or D
Citrate excretion	N	D	D	D	N
In situation of normal acid-base equilibrium (after alkali loading)					
Fractional HCO_3- excretion	>10 to 15%	<5%	>5 to 15%	<5%	>5 to 10%
U-B pCO_2	>20 mmHg	<20 mmHg	<20 mmHg	>20 mmHg	>20 mmHg
Other tubular defects	Often present	Absent	Absent	Absent	Absent
Nephrocalcinosis/lithiasis	Absent	Often present	Often present	Often present	Absent
Bone involvement	Often present	Rarely present	Rarely present	Rarely present	Absent

[Table/Fig-5]: Characteristics of the types of renal tubular acidosis [1].
K+=potassium, NH4=ammonium, Ca=calcium, HCO_3=bicarbonate, U-B pCO_2=urine-blood pCO_2; N=Normal, D=decreased, I=increased

The patient initially presented with a type-2-RTA secondary to vitamin D deficiency which was a reversible cause. Treatment of the reversible defect led to the unmasking of underlying type-4-RTA presenting as refractory hyperkalaemia, NAGMA, mild-moderate renal dysfunction and TTKG of < 2 [1,10]. Other common causes of RTA were ruled out.

The main defect in type-4-RTA is impaired ammoniagenesis producing a defect in distal acidification. Aldosterone deficiency/resistance causes hyperkalaemia which in turn leads to reduced ammonia. Bicarbonate reabsorption can be reduced at a normal serum bicarbonate level, but this reduction is not significant to denote a proximal defect. Hyperkalaemia can be also seen in voltage-dependent type-1-RTA, but unlike this condition, urine acidity is maintained in response to systemic acidosis in type-4-RTA [1].

In this patient, type-4-RTA is due to diabetic nephropathy which was unmasked while treating the initial presentation of type-2-RTA. Use of ACEI in this patient triggered for aggravating the renin-aldosterone system impairment, thereby, precipitating hyperkalaemia of an unrecognised renal tubular defect [13]. Combined proximal/distal RTA is seen in few genetic disorders.

Type-2-RTA presenting on an underlying type-4-RTA is not so common. If present most likely the proximal defect is due to a reversible cause. Thus, caution must be exercised, when treating the proximal defect which can avoid the life-threatening complications of refractory hyperkalaemia, produced by the underlying pathology.

CONCLUSION(S)

In conclusion, co-existence of both type-2 and type-4-RTA is rare but possible. In the present case, initial type-2-RTA was transient and reversible, treatment of which lead to the unmasking of underlying type-4-RTA. The message is that, combined presentation of hypokalaemic and hyperkalaemic RTA can be expected and cautious correction of hypokalaemia is needed so that fatal hyperkalaemia can be prevented in patients, with underlying type-4-RTA. Use of drugs producing hyperkalaemia should also be avoided, in such patients.

REFERENCES

[1] Soriano JR. Renal tubular acidosis: The clinical entity. J Am Soc Nephrol. 2002;13(8):2160-70.
[2] Maddox DA, Deen WM, Gennari FJ. Control of bicarbonate and fluid reabsorption in the proximal convoluted tubule. Semin Nephrol. 1987;7(1):72-81.
[3] DuBose Jr TD. Hyperkalemic hyperchloremic metabolic acidosis: Pathophysiologic insights. Kidney Int. 1997;51(2):591-602.
[4] Sebastian A, Schambelan M, Lindenfeild S, Morris Jr RC. Amelioration of metabolic acidosis with fludrocortisone therapy in hyporeninemic hypoaldosteronism. N Engl J Med. 1977;297(11):576-83.
[5] Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: A not so rare disorder of multiple etiologies. Nephrol Dial Transplant. 2012;27(12):4273-87.
[6] Messiaen T, Deret S, Mougenot B, Bridoux F, Dequiedt P, Dion JJ, et al. Adult Fanconi syndrome secondary to light chain gammopathy. Clinicopathologic heterogeneity and unusual features in 11 patients. Medicine (Baltimore). 2000;79(3):135-54.
[7] Taylor HC, Elbadawy EH. Renal tubular acidosis type 2 with Fanconi's syndrome, osteomalacia, osteoporosis, and secondary hyperaldosteronism in an adult consequent to vitamin D and calcium deficiency: Effect of vitamin D and calcium citrate therapy. Endocr Pract. 2006;12(5):559-67.
[8] Ali Y, Parekh A, Baig M, Ali T, Rafiq T. Renal tubular acidosis type II associated with vitamin D deficiency presenting as chronic weakness. Ther Adv Endocrinol Metab. 2014;5(4):86-89.
[9] Ahmed A, Sims RV. Proximal renal tubular acidosis associated with osteomalacia. South Med J. 2001;94(5):536-39.
[10] Sousa AG, de Sousa Cabral JV, El-Feghaly WB, de Sousa LS, Nunes AB. Hyporeninemic hypoaldosteronism and diabetes mellitus: Pathophysiology assumptions, clinical aspects and implications for management. World J Diabetes. 2016;7(5):101-11.
[11] Yaxley J, Pirrone C. Review of the diagnostic evaluation of renal tubular acidosis. Ochsner J. 2016;16(4):525-30.
[12] Chelaghma N, Oyibo SO. Hyporeninemic hypoaldosteronism in a patient with diabetes mellitus: An unforgettable case report. Int Med Case Rep J. 2018;11:69.
[13] Patzer L. Nephrotoxicity as a cause of acute kidney injury in children. Pediatr Nephrol. 2008;23(12):2159-73.

PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Internal Medicine, PSG Institute of Medical Science and Research, Coimbatore, Tamil Nadu, India.
2. Professor and Head, Department of Internal Medicine, PSG Institute of Medical Science and Research, Coimbatore, Tamil Nadu, India.
3. Professor, Department of Internal Medicine, PSG Institute of Medical Science and Research, Coimbatore, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. S Nirmala,
F5, PSG Doctors Quarters, PSG Hospital Campus, Peelamedu,
Coimbatore-641004, Tamil Nadu, India.
E-mail: nimisekar23@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 22, 2022
- Manual Googling: Jul 27, 2022
- iThenticate Software: Aug 04, 2022 (7%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Mar 08, 2022**
Date of Peer Review: **May 03, 2022**
Date of Acceptance: **Aug 05, 2022**
Date of Publishing: **Nov 01, 2022**