Reminder of important clinical lesson

Primary Sjögren's disease and its complications presenting with progressive paralysis

Matthew Julian,¹ Trishna Chakravorty,² Philip Dyer³¹Critical Care Department, Heartlands Hospital, Birmingham, UK;²Department of Acute Medicine, Heartlands Hospital, Birmingham, UK;³Diabetes and Endocrinology, Diabetes Centre, Heartlands Hospital, Birmingham, UK

Correspondence to Dr Matthew Julian, mattjulian@doctors.org.uk

Summary

A 24-year-old female presented with generalised weakness, lethargy and aches in legs. She was subsequently found to be markedly hypokalaemic and have a metabolic acidosis. A diagnosis of distal renal tubular acidosis (RTA) was made. In addition to this failure to alkalinise her urine, she was unable to concentrate it and so a diagnosis of nephrogenic diabetes insipidus was reached. Further questioning revealed previous investigation of a connective tissue disorder thought to be primary Sjögren's syndrome. RTA is a recognised but rare complication of Sjögren's syndrome. Urinary alkalinisation using potassium bicarbonate was instituted; the patient responded well to treatment and is having outpatient follow-up.

BACKGROUND

This case is important because it is a complex case which might easily be mismanaged and provides a useful educational opportunity to review the management and pathophysiology of renal tubular acidosis (RTA).

CASE PRESENTATION

We report the case of a 24-year-old Asian female who presented to the Department of Acute Medicine with lethargy, generalised weakness with non-specific aches and pains, particularly in her lower limbs.

The limb weakness started 3 days prior to admission, starting in her lower limbs initially and then progressed to her upper limbs. This weakness was associated with sharp pains which progressed from her calf muscles to her thighs. The combination of the weakness and pain resulted in an inability to weight bear.

She had recently returned from a 6-week holiday to Pakistan. During this period she had intermittent loose stools followed by constipation. Since arriving back in the UK she had reported shivers and swinging fever. She also complained of lower abdominal and left flank pain associated with dysuria and urinary frequency.

The patient had a medical history of being investigated for a connective tissue disorder which was thought to be Primary Sjögren's syndrome. There was no other relevant family history.

On physical examination she had a body weight of 101 kg. There were no abnormalities detected on cardiovascular or respiratory examination. Abdominal examination revealed mild abdominal tenderness but no organomegaly or masses. There were no cranial nerve abnormalities. She had bilateral limb weakness which was worse in her lower limbs than upper limbs and distal muscle groups were affected more than proximal. Sensation throughout was intact but reflexes were absent.

INVESTIGATIONS

Laboratory tests performed on admission revealed hypokalaemia (1.8 mmol/l), raised serum urea (8.1 mmol/l) and creatinine (160 µmol/l), high erythrocyte sedimentation rate (ESR) (106 mm/h), hypocalcaemia (1.96 mmol/l) and normal serum sodium. She had a metabolic acidosis (pH 7.14, HCO₃⁻ 11.2 mmol/l and a base deficit -16.8) with a normal lactate and PaCO₂. Urine pH was 7.1. For further results please refer to table 1.

DIFFERENTIAL DIAGNOSIS

A diagnosis of distal RTA was made in the view of hypokalaemic metabolic acidosis and an inability to acidify the urine (see table 1). Further tests revealed vitamin D deficiency (3.8 µg/l, normal >20 µg/l).

TREATMENT

She was transferred to the high-dependency unit for potassium supplementation and observation of the progressive paralysis.

Central venous administration of potassium chloride improved the weakness. Fluid balance charting recorded a consistent urine output of over 150 ml/h. The possibility of nephrogenic diabetes insipidus (NDI) was proposed. To confirm this, a fluid deprivation test was performed. During the deprivation the plasma osmolality rose to 305 mOsm/kg and the urine osmolality was 185 mOsm/kg. After 1-deamino-8-D-arginine vasopressin (desmopressin) the plasma osmolality remained at 304 mOsm/kg and the urine osmolality was 215 mOsm/kg (see table 2). This confirmed the diagnosis of NDI. Careful fluid balance was instituted to prevent hyponatraemia.

Urinary alkalinisation was instituted with potassium bicarbonate for the RTA. Vitamin D supplementation and oral calcium supplementation were commenced for the vitamin D deficiency. The use of a thiazide diuretic for the NDI was considered as a later step.

Table 1 Table of results – sample taken at presentation

Biochemistry		Haematology	
Na 136	133–146	Hb 10.1	11.5–16.0
K1.8	3.5–5.3	WCC 16.29	4.0–11.0
U 8.1	2.5–7.8	Plts 374	150–400
Cr 160	50–110	MCV 84.6	80.0–100.0
eGFR 35		MCH 28.4	27.0–33.0
Cl 121	95–108	Neutrophil 12.92	2.50–7.50
Corrected Ca ²⁺ 1.96 mmol/l	2.20–2.60	ESR 106 mm/h	
Arterial blood gas		Haematinics	
pH 7.14	7.35–7.45	Serum Ferritin 102	13–150
HCO ₃ 11.2 mmol/l	24–28	Folate 7.1	4.6–18.7
Base deficit –16.8		Vitamin B12 252	191–663
Lactate			
Urine pH 7.1			
Autoimmune screen			
Antinuclear antibodies (ANA) positive		Vitamin D 3.8 µg/l	Normal >20
ANA titre 1600			
ENA antibody positive			
ENA specificity positive Ro/SSA			

ENA, extractable nuclear antigen antibodies; ESR, erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; WCC, white cell count

Table 2 Results of fluid deprivation test

Time	Serum osmolality	Urine osmolality
6 h Post-fluid deprivation	305	185
DDAVP 1 h	304	208
2 h	304	215

DDAVP, 1-deamino-8-D-arginine vasopressin (desmopressin).

OUTCOME AND FOLLOW-UP

The patient has had regular follow-up in outpatient clinic following her discharge, at this time it is 18 months since her first presentation and will continue with this follow-up indefinitely. She continues to take potassium carbonate supplementation, along with cholecalciferol as she was found to be deficient in vitamin D. She feels relatively well although has complained of back pain – nephrocalcinosis has been excluded radiologically and is awaiting a DEXA scan to investigate as to whether osteomalacia might be a causative factor.

DISCUSSION

The association of distal RTA with Sjögren's syndrome is well established and purportedly occurs in approximately 30% of patients with Sjögren's syndrome.¹ NDI is also a not infrequent presenting feature.

The hallmarks of RTA are systemic acidosis, hypokalaemia and the inability to lower urine pH below 5.5 despite systemic acidosis. Distal (type 1 or classical) RTA is more common than proximal (type 2) RTA. It can be inherited or acquired, for example, secondarily to hypercalcaemia or autoimmune diseases such as Sjögren's syndrome. It is due to a defect in hydrogen ion excretion and the urine cannot be acidified.² The RTA in Sjögren's syndrome is associated with defects in the H⁺-ATPase. Renal biopsies of affected patients have shown a near absence of H⁺-ATPase in distal tubular cells.³ Consequences include osteomalacia, hypercalciuria, nephrocalcinosis, renal calculi and hypokalaemia. Proximal (type 2) RTA is a component of the Fanconi

syndrome but can also occur as an isolated phenomenon. It is due to an impairment of bicarbonate reabsorption. In this proximal RTA bicarbonate can be completely absorbed if the plasma bicarbonate is low, and thus the patient may excrete normal amounts of acid at the expense of systemic acidosis.²

A history of autoimmune disease and a presentation which includes paralysis should include a differential of hypokalaemic paralysis secondary to distal RTA. A worsening paralysis with risk of respiratory failure and also potential arrhythmia should warrant management in a critical care facility with appropriate monitoring and the availability to step to ventilatory support. Paralysis is believed to occur secondary to a change in the ratio between the intracellular versus the extracellular potassium concentration which leads to membrane depolarisation affecting excitable tissues, although the central nervous system is spared due to the blood brain barrier.^{4 5} Progressive paralysis is often misdiagnosed as Guillain-Barré syndrome until the serum potassium is known. The long-term management after the initial correction of the metabolic disturbance is alkalinisation and additional supplementation (eg, potassium and magnesium).

NDI is characterised by a decrease in the ability to concentrate urine due to a resistance to antidiuretic hormone action in the kidney. NDI can be observed in chronic renal insufficiency, lithium toxicity, hypercalcaemia, hypokalaemia and tubulointerstitial disease; rarely NDI may be hereditary. In our case hypokalaemia was present. In animals, hypokalaemia can induce NDI by a downregulation of aquaporin-2 water channel expression secondary to decreased cyclic AMP production⁶ although reduced expression of additional renal transporters further upstream might also contribute.⁷ Treatment of NDI requires careful and tailored intravenous fluid therapy to prevent hyponatremia caused by a negative water balance or a positive sodium balance.

The combination of distal RTA and NDI is uncommon but has been seen during treatment with amphotericin B.⁸

Table 3 Diagnosis of renal tubular acidosis

Procedure	Result
Take blood for bicarbonate measurements after overnight fast	Measure pH of freshly passed urine: If pH <5.5, RTA is excluded If pH >5.5, RTA and plasma HCO ₃ <16 mmol/l, RTA is diagnosed If pH >5.5, RTA and plasma HCO ₃ >16 mmol/l perform urinary acidification test
Urinary acidification test Give ammonium chloride – 100 mg/kg orally	Normal response: urine pH <5.2 in at least one sample If this pH is not obtained test should be repeated if serum bicarbonate is not below the lower limit of normal
Measure pH of freshly passed urine hourly for 8 h	Type 1 RTA urine pH ≥ 6.5
RTA, renal tubular acidosis.	

Learning points

- Sjögren's disease can present as RTA.
- Appears to be secondary to absence of functional H⁺-ATPase from distal renal tubule.
- Management of type 1 RTA requires urinary alkalinisation with potassium bicarbonate.
- NDI requires careful fluid management with monitoring of electrolytes to prevent hypernatraemia.

Amphotericin B can cause NDI by impairing the expression of aquaporin-2 water channels through an effect on adenylyl cyclase.⁹ and amphotericin B causes RTA by increasing membrane permeability in the collecting duct, resulting in a back-flux of H⁺ ions¹⁰ (namely, adenylyl cyclase V) which regulates vacuolar H⁺ ATPase, which is the main transporter responsible for H⁺ ion secretion in the renal collecting duct.¹¹

Several diseases and drugs can perturb renal tubular function in different nephron segments, potentially resulting in acid-base or electrolyte disorders. RTA should be suspected in all patients who present with a non-anion-gap metabolic acidosis, hypokalaemia and a high urinary pH, in the absence of gastrointestinal bicarbonate loss (table 3). NDI should be suspected when vasopressin-resistant polyuria with a low urinary osmolality develops.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Siamopoulos KC**, Elisaf M, Drosos AA, *et al.* Renal tubular acidosis in primary Sjögren's syndrome. *Clin Rheumatol* 1992;**11**:226–30.
2. **Soriano JR**. Renal tubular acidosis: the clinical entity. *J Am Soc Nephrol* 2002;**13**:2160–70.
3. **DeFranco PE**, Haragsim L, Schmitz PG, *et al.* Absence of vacuolar H(+)–ATPase pump in the collecting duct of a patient with hypokalemic distal renal tubular acidosis and Sjögren's syndrome. *J Am Soc Nephrol* 1995;**6**:295–301.
4. **Ahlawat SK**, Sachdev A. Hypokalaemic paralysis. *Postgrad Med J* 1999;**75**:193–7.
5. **Lin SH**, Davids MR, Halperin ML. Hypokalaemia and paralysis. *QJM* 2003;**96**:161–9.
6. **Marples D**, Frøkiaer J, Dørup J, *et al.* Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. *J Clin Invest* 1996;**97**:1960–8.
7. **Elkjær M-L**, Kwon TH, Wang W, *et al.* Altered expression of renal NHE3, TSC, BSC-1, and ENaC subunits in potassium-depleted rats. *Am J Physiol Renal Physiol* 2002;**283**:1376–88.
8. **Hoorn EJ**, Zietse R. Combined renal tubular acidosis and diabetes insipidus in hematological disease. *Nat Clin Pract Nephrol* 2007;**3**:171–5.
9. **Kim SW**, Yeum CH, Kim S, *et al.* Amphotericin B decreases adenylyl cyclase activity and aquaporin-2 expression in rat kidney. *J Lab Clin Med* 2001;**138**:243–9.
10. **Rose BD**, Post TW. *Clinical Physiology of Acid–Base and Electrolyte Disorders*. Fifth edition. New York: McGraw-Hill 2001.
11. **Héliès-Toussaint C**, Aarab L, Gasc JM, *et al.* Cellular localization of type 5 and type 6 ACs in collecting duct and regulation of cAMP synthesis. *Am J Physiol Renal Physiol* 2000;**279**:F185–94.

This pdf has been created automatically from the final edited text and images.

Copyright 2010 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Julian M, Chakravorty T, Dyer P. Primary Sjögren's disease and its complications presenting with progressive paralysis. *BMJ Case Reports* 2010;10.1136/bcr.09.2010.3347, date of publication

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow