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BRIEF REPORT

Flaccid paresis due to distal renal tubular acidosis preceding systemic lupus erythematosus

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ABSTRACT

We report a 25-year-old woman presenting with a flaccid paresis due to severe hypokalaemia as a consequence of distal renal tubular acidosis (dRTA). Six years after presentation of dRTA, she developed overt symptoms of systemic lupus erythematosus (SLE). dRTA in SLE is often secondary to an interstitial nephritis. In contrast to other reports the dRTA did not resolve after treatment with prednisone in our patient. Nephrocalcinosis might be one of the causal factors in the persistence of dRTA.

INTRODUCTION

Distal renal tubular acidosis (dRTA) is associated with hypercalciuria, exposition to tubulotoxic agents and with several autoimmune diseases such as Sjögren's syndrome and, less commonly, systemic lupus erythematosus (SLE).[1] We report a patient presenting with a flaccid paresis due to hypokalaemia as a consequence of dRTA. Six years after presentation of dRTA, she developed overt symptoms of SLE. Such a long time interval is very rare. Up until now, the longest reported time interval between presentation of dRTA and SLE was four years.[2] Also, in retrospect, dRTA seems to be the first symptom of SLE in our patient.

CASE REPORT

A 25-year-old slender woman presented with an episodic flaccid paresis of the extremities in 1990. On several occasions she was unable to walk, and she dropped cups. These symptoms came and went over a period of approximately one year.

On hospital admission her weight was 45 kg, the blood pressure was 95/60 mmHg and pulse rate 80 beats/min. There was a flaccid paresis of the extremities with intact reflexes. On laboratory examination, the ESR was 60 mm in the first hour, serum potassium 2.0 mmol/l, sodium 141 mmol/l, chloride 118 mmol/l, and creatinine 117 μmol/l. In venous blood the pH was 7.17, PCO_2 5.5 kPa and bicarbonate concentration 14.9 mmol/l. The calculated anion gap (Na^+ - ($HCO3^-$ + Cl^-), normal value 5-11 μmol/l) was 8 mmol/l. Haematological parameters as well as values for serum ASAT and ALAT were within normal limits. Serological tests revealed absent antinuclear antibodies and normal values for complement C3 and C4.

Laboratory analysis of the urine revealed concentrations of sodium of 28 mmol/l, potassium of 27 mmol/l, and chloride of 55 mmol/l. The calculated urinary anion gap (Na^+ + K^+, - Cl^-) for estimating urinary ammonium excretion) was zero mmol/l.[3] The pH of the urine was above 7. After an acid load of 0.1 gram /kg NH_4Cl, the urinary pH decreased from 6.8 to 6.4 (normal <5.3). The maximum urinary calcium excretion was 5 mmol/day during acidosis, but usually below 2 mmol/day (normal value <5 mmol/day). The calculated creatinine clearance was approximately 48 ml/min. There was a slight proteinuria (±0.2 gram/day) and leucocyturia without bacteriuria. Glomerular casts were not seen on light microscopic examination. Extensive work-up for analysis of the raised ESR including urine cultures, CT abdomen, radiographic barium contrast study of the colon and terminal ileum and gynaecological examination revealed no abnormalities.

The presence of nephrolithiasis or nephrocalcinosis was not mentioned in the reports of the radiological examinations.

In conclusion, there was an incompetence of excreting ammonium during acidaemia. A diagnosis of complete dRTA with hypokalaemic paresis was made. No primary cause was found for dRTA, so by definition it was classified as idiopathic dRTA. Besides, there was no explanation for the decreased renal function and the raised ESR. After institution of chronic suppletion of sodium bicarbonate 4 gram/day (±1 mmol/kg/day) and potassium chloride (±0.5 mmol/kg/day) the paresis disappeared.

Between 1990 and 1996 she was admitted to the hospital several times with recurrent symptoms of dRTA which rapidly responded to oral suppletion of sodium bicarbonate and potassium chloride. The main problem seemed compliance with the medication, since she could not tolerate the sodium bicarbonate due to gastrointestinal complaints. An abdominal X-ray taken in 1993 now revealed nephrocalcinosis of both kidneys (*figure 1a*). She passed small stones with her urine on several occasions. She experienced several (ascending) urinary tract infections requiring treatment with antibiotics. The concentration of citrate in the urine was <0.10 mmol/l (normal value 0.5-4.0 mmol/l).

In August 1996 she was readmitted with high fever, arthralgia of both ankles and a butterfly shaped rash on the face after a holiday in Spain. Again she presented with metabolic acidosis and hypokalaemia. There was a thrombocytopenia of 90 x 10^{-9}/l and the complement levels were low: C3: 594 mg/l (normal value: 750-1250 mg/l) and C4: 171 mg/l (normal value: 180-400 mg/l). Serological tests revealed antinuclear antibodies, anti double-stranded DNA antibodies (titre 1:20), and antibodies (ENA) against SS-A. Urinalysis was unchanged with persistent leucocyturia and a slight proteinuria (maximum 0.8 g/l). Glomerular casts were not seen on light microscopic examination. The serum creatinine level was unchanged. The patient refused a renal biopsy. There were no buccal ulcers, no neurological symptoms and there were no enlarged lymph nodes. In conclusion, besides a recurrence of the renal tubular acidosis five ARA criteria were positive, confirming the diagnosis of SLE (butterfly rash, arthralgia, thrombocytopenia, positive ANA and double-stranded DNA antibodies).[4]
Because of severe constitutional symptoms a trial of prednisone 30 mg was started. There was a remarkable improvement of her clinical condition. Although the metabolic acidosis initially seemed to improve after starting prednisone, it recurred (*figure 2*). After tapering the prednisone dose to zero the constitutional symptoms returned, and it was decided to restart the prednisone at 10 mg a day. An X-ray of the abdomen taken in 2000 showed an increase in the *nephrocalcinosis* (*figure 1b*). The creatinine clearance decreased only slightly from ±48 ml/min in 1990 to ±44 ml/min in 2000. Bone mineral density, as measured by dual energy X-ray absorptiometry, performed after one year of steroids, revealed osteopenia of the spine and severe osteoporosis of the right hip. Unfortunately, she broke her hip after a minor accident after four years of treatment with prednisone at the age of 35.

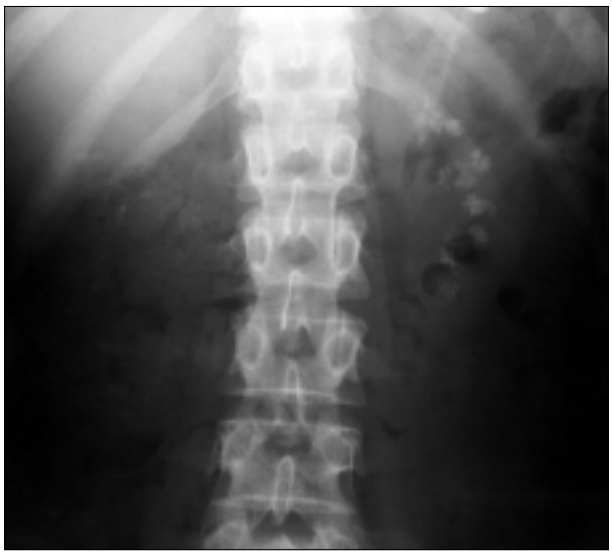

Figure 1a

X-ray of the abdomen taken in 1993, showing severe bilateral nephrocalcinosis three years after diagnosis of distal renal tubular acidosis.

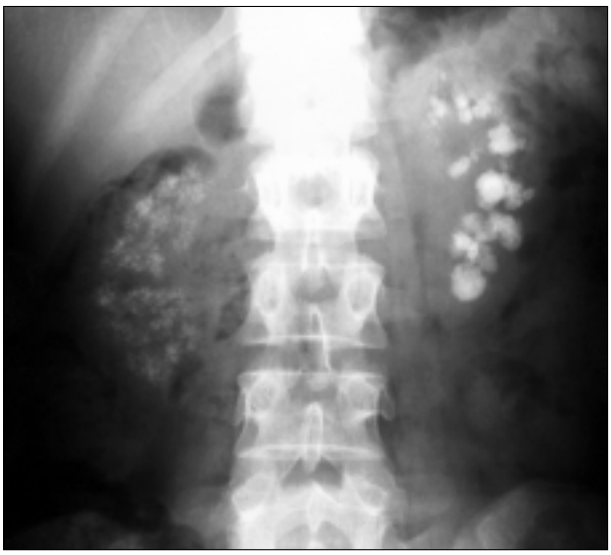

Figure 1b

An X-ray taken in 2000 showed an impressive increase of the nephrocalcinosis.

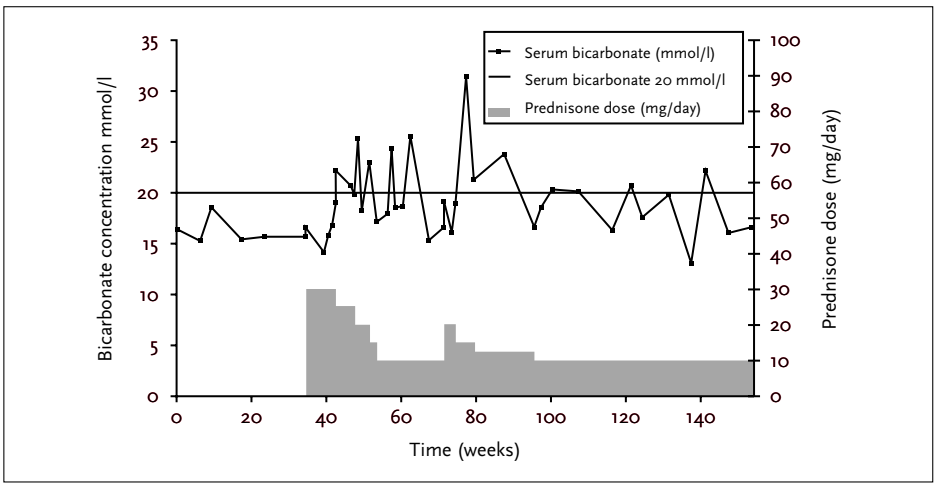

Figure 2

Treatment with prednisone did not cure distal renal tubular acidosis in our patient. Although the serum concentration of bicarbonate seemed to normalise after starting prednisone, it remained low later on.

DISCUSSION

We have presented a patient with a flaccid paresis due to severe hypokalaemia as a consequence of a complete dRTA. Frequently dRTA is associated with hypercalciuria and subsequent nephrocalcinosis, but is also well described in autoimmune diseases such as Sjögren's and SLE.[1] In our patient there was no hypercalciuria when acidosis was corrected and nephrocalcinosis (and nephrolithiasis) became clinically apparent several years after the diagnosis of dRTA. So both hypercalciuria and nephrocalcinosis have to be considered as a consequence and not a cause of dRTA in our patient. As long as six years after the diagnosis of dRTA, other symptoms of SLE became apparent. In retrospect, it is tempting to suggest that hypokalaemic dRTA was the first symptom of SLE in our patient. The unexplained raised ESR at presentation is compatible with this suggestion.

In the literature dRTA has been extensively reviewed.[5, 6] It is characterised by a hyperchloraemic metabolic acidosis accompanied by a reduced renal net acid excretion and the inability to lower the pH of the urine under 5.5 during acidaemia. The defect in ammonium and titratable acid excretion impairs the acidification of the urine and results in acidaemia. The decreased ammonium excretion as calculated with a zero urinary anion gap in our patient during acidaemia as well as the diminished lowering of the pH after an acid load is compatible with this type of dRTA. In contrast to dRTA, in proximal renal tubular acidosis the ability of acidification of the urine is maintained. So, in the latter condition, the urinary anion gap is negative during acidaemia and the urinary pH decreases after an acid load in these patients. Proximal renal tubular acidosis is characterised by a reduced reabsorption of bicarbonate in the proximal tubules. Patients with dRTA often have hypokalaemia as a result of excessive urinary excretion of potassium, but also hyperkalaemic variants occur.[7, 8] Muscle weakness is a well-known symptom of hypokalaemia, and several patients with severe hypokalaemia complicated by paresis and even respiratory arrest have been described.[2, 9] Many patients with hypokalaemic dRTA have hypercalciuria and hyperphosphaturia as a consequence of the buffering of chronic acidaemia by bones and many such patients develop nephrocalcinosis.[10] Calcium phosphate precipitation in the kidney is promoted by a high urinary pH and hypocitraturia.[11] Chronic acidaemia decreases the renal excretion of citrate.

SLE is associated with a variety of tubular defects. When tested in patients with acute exacerbations of SLE, 60% have a distal tubular acidification defect.[12] Approximately 2-30% of patients with SLE have a complete, although often asymptomatic, dRTA with systemic acidaemia.[8, 12] It has been suggested that these patients have an overlap-syndrome of Sjögren's syndrome and SLE, since some patients (like our patient) have antibodies against ENA-SS.[8] Our patient however, did not have clinical signs of Sjögren's syndrome.

Renal biopsy of patients with dRTA and SLE generally shows interstitial nephritis although a correlation between tubular (dys)function and the degree of histological interstitial lesions is usually absent.[12, 13] The persistent leucocyturia and the slight proteinuria without glomerular casts in our patient are fitting with the diagnosis of isolated interstitial nephritis. However, histological proof is lacking, and also nephrocalcinosis can be associated with proteinuria.[14] In our opinion a renal biopsy is indicated for guidance of the immunosuppressive therapy in such patients, especially in case of renal failure or significant proteinuria, where concomitant glomerulonephritis requires more intensive immunosuppression. Immunohistochemical studies in patients with hypokalaemic dRTA and SLE have not been performed yet, but in patients with hypokalaemic dRTA and Sjögren's syndrome an absence of H^+-ATPase in the intercalated cells in the distal tubules has been demonstrated.[15] The absence of H^+-ATPase restrains

excretion of H^+ and thus impairs the formation of urinary ammonium and the excretion of ammonium with the urine. Whether the absence of H^+-ATPase is the result of a generalised dysfunction of the intercalated cells or of a specific immunological destruction of H^+-ATPase is not known.

Adequate treatment of the primary cause of dRTA (withdrawal of the toxic agent) potentially cures dRTA. A causal treatment of the primary cause is not always possible and the interstitium might become irreversibly damaged due to the primary cause or due to long-standing dRTA (nephrocalcinosis). Therefore, symptomatic correction of the chronic acidaemia is the mainstay of treatment in such cases of dRTA. Restoring the acidaemia with sodium bicarbonate (±1-2 mmol/kg) and especially (potassium) citrate is known to prevent nephrocalcinosis, urolithiasis and probably also osteoporosis.[16] Hypokalaemia in dRTA is also corrected by restoring acidaemia, sometimes potassium suppletion is not even necessary. Suppletion of potassium without correction of the acidosis leads to recurrent hypokalaemia as a result of ongoing urinary potassium wasting.[7] The inability of the distal tubular cells to establish a steep lumen/peritubular H^+ gradient reduces the rate of H^+/Na^+ exchange. Consequently, more potassium is secreted in exchange of sodium to maintain intraluminal electroneutrality.

In patients with SLE and Sjögren's syndrome treatment of the interstitial nephritis with steroids can restore renal tubular acidosis.[2, 17] In our patient treatment with steroids only had a marginal effect on the acidosis, while the serum bicarbonate remained low (*figure 2*). Of course, this resistance of dRTA to treatment with glucocorticoids might be due to a diffuse and irreversible destruction of the tubular interstitium. The resistance of dRTA to glucocorticoids in our patient therefore required (aggressive) symptomatic treatment with alkali therapy to prevent complications of dRTA. Unfortunately, neither sodium bicarbonate nor potassium citrate were tolerated by our patient, leading to all the known complications related to untreated dRTA. The slow deterioration of the renal function is presumably due to recurrent ascending urinary tract infections related to the extended nephrocalcinosis and nephrolithiasis, in combination to chronic interstitial nephritis.

In conclusion, distal renal tubular acidosis can be the first manifestation of SLE preceding other symptoms of SLE by years. dRTA in SLE is usually the result of interstitial nephritis. In contrast to earlier reports the dRTA in our patient did not respond to treatment with prednisone. This may be the result of long-standing interstitial nephritis as well as of concomitant nephrocalcinosis. Therefore, symptomatic correction of the chronic acidaemia with alkali therapy was required. Unfortunately, our patient did not tolerate alkali therapy. The persistent dRTA led to recurrent symptomatic hypokalaemia, progressive nephrocalcinosis, frequent urolithiasis, renal insufficiency and in combination with the long-term use of glucocorticoids to an osteoporotic fracture.

REFERENCES

1. Caruana RJ, Buckalew VMJ. The syndrome of distal (type 1) renal tubular acidosis. Clinical and laboratory findings in 58 cases. Medicine Baltimore 1988:67:84-99.
2. Bagga A, Jain Y, Srivastava RN, Bhuyan UN. Renal tubular acidosis preceding systemic lupus erythematosus. Pediatr Nephrol 1993:7: 735-6.
3. Goldstein MB, Bear R, Richardson RM, Marsden PA, Halperin ML. The urine anion gap: a clinically useful index of ammonium excretion. Am J Med Sci 1986:292:198-202.
4. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982:25:1271-7.
5. Batlle D, Flores G. Underlying defects in distal renal tubular acidosis: new understandings. Am J Kidney Dis 1996:27:896-915.
6. Smulders YM, Frissen PH, Slaats EH, Silberbusch J. Renal tubular acidosis. Pathophysiology and diagnosis. Arch Intern Med 1996:156: 1629-36.
7. Sebastian A, McSherry E, Morris RCJ. Renal potassium wasting in renal tubular acidosis (RTA): its occurrence in types 1 and 2 RTA despite sustained correction of systemic acidosis. J Clin Invest 1971:50:667-78.
8. Graninger WB, Steinberg AD, Meron G, Smolen JS. Interstitial nephritis in patients with systemic lupus erythematosus: a manifestation of concomitant Sjögren's syndrome? Clin Exp Rheumatol 1991:9:41-5.
9. Poux JM, Peyronnet P, Meur Y le, Favereau JP, Charmes JP, Leroux RC. Hypokalemic quadriplegia and respiratory arrest revealing primary Sjögren's syndrome. Clin Nephrol 1992:37:189-91.
10. Brenner RJ, Spring DB, Sebastian A, et al. Incidence of radiographically evident bone disease, nephrocalcinosis, and nephrolithiasis in various types of renal tubular acidosis. N Engl J Med 1982:307:217-21.
11. Norman ME, Feldman NI, Cohn RM, Roth KS, McCurdy DK. Urinary citrate excretion in the diagnosis of distal renal tubular acidosis. J Pediatr 1978:92:394-400.
12. Kozeny GA, Barr W, Bansal VK, et al. Occurrence of renal tubular dysfunction in lupus nephritis. Arch Intern Med 1987:147:891-5.
13. Borg EJ ter, Jong PE de, Meijer SS, Kallenberg CG. Tubular dysfunction in proliferative lupus nephritis. Am J Nephrol 1991:11:16-22.
14. Langlois V, Bernard C, Scheinman SJ, Thakker RV, Cox JP, Goodyer PR. Clinical features of X-linked nephrolithiasis in childhood. Pediatr Nephrol 1998:12:625-9.
15. Cohen EP, Bastani B, Cohen MR, Kolner S, Hemken P, Gluck SL. Absence of H(+)-ATPase in cortical collecting tubules of a patient with Sjögren's syndrome and distal renal tubular acidosis. J Am Soc Nephrol 1992:3:264-71.
16. Preminger GM, Harvey JA, Pak CY. Comparative efficacy of "specific" potassium citrate therapy versus conservative management in nephrolithiasis of mild to moderate severity. J Urol 1985:134:658-61.
17. Mallakh RS el, Bryan RK, Masi AT, Kelly CE, Rakowski KJ. Long-term low-dose glucocorticoid therapy associated with remission of overt renal tubular acidosis in Sjögren's syndrome. Am J Med 1985:79:509-14.