

SJÖGREN'S SYNDROME PRESENTING WITH HYPOKALEMIC PARALYSIS DUE TO RENAL TUBULAR ACIDOSIS

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Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration, as well as destruction of exocrine glands. The syndrome is characterized by keratoconjunctivitis sicca (KCS) and xerostomia, with or without parotid gland enlargement.¹ It is frequently associated with connective tissue diseases. Impaired urinary acidification, chronic renal failure and tubulointestinal nephritis have been described in SS. Renal tubular acidosis (RTA) is estimated to be present in 25%-30% of cases with SS.² SS patients presenting with flaccid quadriplegia due to hypokalemia associated with RTA are rare.³ We report two patients with SS and resultant RTA whose initial sole presentation was quadriplegia due to severe hypokalemia.

Case Report

Case 1

A 15-year-old female was brought to our hospital emergency room with total inability to move any of her four limbs for the previous four hours. She had had muscle pain and cramps eight hours prior to the onset of the paralysis. A year earlier, she had suffered recurrent episodes of purpuric lesions in the legs and was found to have proteinuria of 0.5 g/day, for which she had been investigated elsewhere. Biochemical, serological, bacteriological and radiological workup had been reported as normal at this point. This time the patient had no abdominal pain, arthralgia, hematuria, alopecia or photosensitivity to suggest collagen diseases. She denied any recent history of cough, fever, urinary symptoms, dysphagia, visual abnormalities, convulsions or trauma. She had had dryness of the eyes and mouth for the previous six months prior to the onset of the present symptoms. She denied any recent history of specific drug therapy or symptoms suggestive of myasthenia gravis.

Physical examination of the patient was unremarkable except for the neurological findings. Her muscle power was 1/5 in the neck flexors and extensors and all muscles of both upper and lower extremities. Examination of the sensory system was normal. All reflexes were symmetrically sluggish and plantar responses were flexor. The optic fundi were normal. The immediate laboratory investigations revealed severe hypokalemia (1.4 mmol/L), severe acidosis (arterial blood pH 7.262, PaCO₂ 4.3 kPa, HCO₃ 11.4 mmol/L), normal blood sugar (5.8 mmol/L), and an alkaline urine (urine pH 7.24). Her serum creatinine (62 µmol/L), urea (5.1 mmol/L), sodium (138 mmol/L), chloride (108 mmol/L), calcium (2.3 mmol/L), phosphate (0.9 mmol/L), magnesium (0.74 mmol/L) and liver function tests were all normal. A diagnosis of RTA with severe hypokalemia leading to paralysis was made. She was treated with adequate bicarbonate and potassium supplements and her weakness completely disappeared during the next forty-eight hours.

The patient underwent detailed laboratory evaluation to delineate the type of RTA and to define its etiology. She had anemia (Hb 10.8 g%, PCV 31%), with normal platelet and leukocyte count. Coagulation parameters were normal, and indirect and direct Coomb's tests were negative. The serological results and 24-hour urinary excretion parameters are given in Tables 1 and 2, respectively. Urine examination revealed no microhematuria and was sterile on culture. Urine specific gravity (1023) and osmolality (380 mOsm/kg water) were normal. Since the urine was highly alkaline in the presence of severe acidosis at presentation, an ammonium chloride loading test was not performed. Schirmer's test was positive in both eyes (wetting <5 mm), and an ophthalmic evaluation revealed reduced, poor and unstable tear film with evidence of exposure keratitis. The parotid radionuclear scintigraphy showed decreased tracer uptake by parotid and sublingual glands bilaterally. On stimulation with lemon juice the parotid gland showed minimal response. A percutaneous needle renal biopsy and histological evaluation demonstrated interstitial lymphoplasmacytic infiltration with tubulitis and sheets of foamy macrophages containing PAS-positive material. The tubular cells showed vacuolation and some disruption with focal

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TABLE 1. Immunological and other important laboratory data.

Values

Parameters	Case 1	Case 2	Normal
Antinuclear antibody	>1/20 speckled pattern	>1/20 speckled pattern	-
Anti DsDNA antibody	Negative	Negative	-
Anti Sm antibody	Negative	Negative	-
SS-A/Ro precipitin	Positive	Positive	-
SS-B/La precipitin	Positive	Positive	-
Anti RNP antibody	Negative	Negative	-
C ₃ (g/L)	0.93	1.59	0.5-1.2
C ₄ (g/L)	0.29	0.49	0.2-0.5
C-reactive protein	Positive	Negative	-
Rheumatoid factor	1/320 positive	1/20 positive	-
ASOT	Up to 200 todd units	Negative	-
Total protein (g/L)	90.5	92.1	63-80 g/L
Albumin (g/L)	34.8	45	37-47 g/L
Globulin (g/L)	55.7	46.2	26-33 g/L
IgM (g/L)	5.7	6.1	0.45-2.6 g/L
IgA (g/L)	3.8	3.7	0.81-2.3 g/L
IgG (g/L)	30.3	33.8	7-16.5 g/L
Cryoglobulin	Negative	Negative	Negative
ESR (mm/hr)	82	115	<10 mm/Hg
HLA*	A9(23), A9(24) B18, B41, Bw6, Cw blank, <i>DR₃</i> , <i>DR5(11)</i> , <i>DR52</i> <i>DQ₂</i> , <i>DQ3</i>	A2, A4, B ₃ , B ₈ , C ₄ , <i>DR₃</i> , <i>DR_w52</i>	

*In italic are the common antigens known to occur in primary SS.

TABLE 2. Daily excretion of urinary parameters.

Parameters	Values/day		
	Case 1	Case 2	Normal
Proteins (g)	0.715	0.124	<0.150
Glucose (mmol)	0.4	0.88	0.3-1.7
Phosphate (mmol)	13.2	18.5	12.9-42.0
Calcium (mmol)	1.43	3.1	<3.8
Chloride (mmol)	140	128	125-250
Sodium (mmol)	102	108	100-260
Potassium (mmol)	28	42	25-100
Urate (mmol)	3.2	2.8	1.48-4.43
Aminoaciduria	Not detected	Not detected	-
Creatinine (mmol)	3.2	6.8	3-10

nephrocalcinosis, while blood vessels were normal. These findings confirmed the the diagnosis of primary Sjögren's syndrome, interstitial nephritis and distal RTA.

TABLE 3. Review of the reported cases in the literature, showing presentation, renal disease, treatment and outcomes.

The patient was first treated with intravenous potassium and bicarbonate supplements. After symptomatic recovery she was maintained on regular Shohl's solution and potassium tablets. She became stable and is on regular outpatient follow-up.

Case 2

A 52-year-old female presented to our emergency department with an eight-hour history of severe muscle weakness and inability to move. She had had mild pain in the arms and thighs 24 hours earlier. She had dryness of mouth and eyes but denied any history of cough, urinary symptoms, abdominal pain, dysphagia, convulsions, photosensitivity, purpuric lesions, arthralgia, alopecia or intake of any drugs. She denied any history suggestive of myasthenia gravis.

Physical examination revealed a severely weak female who could not move any of her limbs. Her blood pressure (120/70 mm Hg), pulse (70/min.), and respiratory rate (22/min.) were all normal. She was afebrile and had bilateral parotid gland enlargement and generalized ichthyosis of the skin. Examination of the cardiovascular and respiratory systems and abdomen did not reveal any abnormal findings. Muscle power was very weak (1/5) in the proximal muscles of all four extremities compared to distal muscles (2/5). Sensations were intact all over, while deep reflexes were absent and plantar response was flexor. The optic fundi were normal. Immediate investigations revealed severe hypokalemia (serum potassium 1.5 mmol/L) and acidosis (arterial blood pH 7.28, PaCO₂ 4.2 kPa, HCO₃ 9.5 mmol/L, PaO₂ 11.2 kPa). Serum sodium (145 mmol/L), chloride (113 mmol/L), magnesium (0.78 mmol/L), calcium (2.4 mmol/L), sugar (5.9 mmol/L), and creatinine phosphokinase (42 U/L) were all normal. Electrocardiogram showed prominent U-waves. A spot urine pH was 7.5. The electrolyte disturbances were corrected with adequate potassium, bicarbonate and fluid specimens. All the clinical manifestations gradually disappeared. A diagnosis of severe hypokalemic paralysis due to RTA was made. She underwent detailed laboratory investigations to confirm RTA and to define its etiology. These revealed mild anemia (Hb 9.2 g%, PCV 29%), and normal leukocyte and platelet counts. The serological results and 24-hour urinary excretion parameters are given in Tables 1 and 2, respectively. She did not have microscopic hematuria, and urine was sterile on culture. After stopping the treatment for 48 hours, an ammonium chloride loading test was performed, which showed failure to acidify the urine below pH 6.27 at a time of severe acidosis (arterial blood pH 7.26). Schirmer's test was positive (wetting of 4 mm) in both eyes. A fine-needle aspiration cytology of the parotid gland showed diffuse lymphocytic infiltration of the gland. A renal biopsy was refused by the patient. She was maintained on oral potassium citrate solution and sodium bicarbonate capsules and has remained asymptomatic since.

Ref .no.	Clinical presentation	Degree of hypokalemia (serum K+mmol/L)	Degree of acidosis (pH)	Renal histology	Treatment and response
3	Flaccid quadriplegia, respiratory arrest, acidosis, hypokalemia	1.4	7.13	Tubulointerstitial disease with tubular atrophy and diffuse lymphocytic and plasma cell infiltration	Bicarbonate and potassium supplements Recovered
4	Slow-onset quadriplegia, dysphagia, dysphonia, irritation of eyes and parotid swelling	1.0	7.26	ND	Bicarbonate and potassium supplements + spiranolactone Recovered
5	1) Pain in legs, muscle weakness	2.5	7.26	Tubulointerstitial lymphocytic and plasma cell infiltration	Sodium and potassium citrate Recovered
	2) Muscle weakness followed by five episodes of quadriplegia	2.3	7.28	Interstitial fibrosis with lymphocytic and plasma cell infiltration	Sodium and potassium citrate Recovered
		2.6	7.33	Lymphocytic infiltration of round cells	Alkali preparation Recovered
	3) Quadriplegia	2.1	7.32	Interstitial fibrosis and lymphocytic infiltration	Sodium potassium citrate Recovered
4) Muscle weakness, quadriplegia					
7	Muscle weakness, quadriplegia	2.8	7.37	–	Oral Shohl's solution and potassium chloride Recovered
8	1) Flaccid paralysis of all 4 limbs	1.2	7.31	Interstitial infiltration with plasma cells and lymphocytes with tubular atrophy	Potassium and alkaline supplements Recovered
	2) Paralysis	2.4	7.24	–	Sodium bicarbonate and potassium supplements Recovered
9	Quadriplegia	1.8	7.2	–	Alkali and potassium supplements
10	Nausea, vomiting, dysphagia, history of paralysis 3 years before	2.3	7.15	–	Sodium bicarbonate and potassium supplements Recovered
11	Xerostomia, xerophthalmia, flaccid quadriplegia	1.5	7.36	–	IV potassium and sodium bicarbonate Recovered
12	Progressive muscle weakness, vomiting	1.8	7.30	Interstitial infiltration of lymphocytes and plasma cells	IV potassium chloride and sodium bicarbonate Recovered
13	Progressive muscle weakness	1.9	7.35	–	IV and oral potassium chloride Recovered
PR *	1) Muscle pain, quadriplegia	1.4	7.26	Interstitial lympho- and plasmacytic infiltration, tubulitis, sheets of foamy macrophages, tubular vacuolation and nephrocalcinosis	IV sodium bicarbonate and potassium chloride followed later by Shohl's solution and potassium tablets Recovered
	2) Muscle pain, dryness of eyes and weakness of all 4 limbs	1.5	7.28	–	IV sodium bicarbonate and potassium chloride followed by oral potassium citrate tablets Recovered

*PR=present report.

Discussion

The two cases demonstrate that primary SS may present with life-threatening complications of hypokalemia due to renal involvement. Hypokalemia, metabolic acidosis and inappropriate urine pH in our patients suggest a diagnosis of RTA. The presence of normal proximal tubular functions and the failure to acidify urine upon ammonium chloride loading supports a diagnosis of distal RTA. Acid loading is especially useful in bringing out latent forms of distal RTA, while overt forms are obvious at the time of initial

presentation.⁵ Adult onset distal RTA due to autoimmune disease, especially when associated with SS, is predominantly a disease of women.⁵ Both patients in this report are female.

The diagnosis of SS was established in our cases according to the Copenhagen criteria and European preliminary classification criteria.¹ Both our patients had keratoconjunctivitis sicca and xerostomia. In addition, detailed clinical, immunological and serological studies have helped to rule out connective tissue or other autoimmune diseases that could produce SS.

Symptomatic RTA is rare in primary SS and is often latent.² Other tubular functional abnormalities, such as aminoaciduria and nephrogenic diabetes insipidus, are also described in SS. Our patients have only isolated distal RTA. Pathogenesis of distal RTA in SS is debated. Hypergammaglobulinemia,² interstitial and tubular lymphocytic infiltration,⁵ and increased renal tubular cytotoxic (CD 8) T-lymphocytic infiltration³ have all been implicated. It has been shown that the renal tubular dysfunction is irreversible and does not respond to adrenocorticosteroids.⁵ At two years' follow-up, both patients continue to require supplement therapy, which supports the above observation.

The most common renal pathology in SS is interstitial nephritis, as was demonstrated in our first patient. Immune complex membranous or membranoproliferative glomerulonephritis is rare and occurs in association with cryoglobulinemia and/or vasculitis. It has been shown using immunohistochemical methods that a similar immunological process leading to mononuclear cell infiltration is operative both in the kidney and salivary gland in SS.⁶ It has been reported that occurrence of RTA is dependent upon the degree and distribution of renal changes.⁵ However, RTA can occur in SS without any demonstrable histological abnormalities, while interstitial changes may be seen without consequent RTA.⁵

Sudden life-threatening hypokalemia with muscle paralysis is the most serious clinical consequence of distal RTA.⁴ Warning symptoms of muscle weakness, psychic apathy and lethargy are often present for months or years before muscle paralysis occurs.⁵ Neither patient in this report observed any early warning symptoms, except for muscle pains for a few hours prior to the onset of paralysis. Periodic paralysis had been reported earlier in a patient with distal RTA due to SS.⁷

To our knowledge, only 14 cases of distal RTA with hypokalemic muscle paralysis have been previously reported in SS.^{3,4,5,7-13} These reported cases have many similarities with our two patients. Except for one patient,⁷ all others had underlying primary SS. Delays of anywhere from three months⁹ to five years⁵ from the onset of initial

clinical manifestation have been reported before a diagnosis of SS is established.

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