

# Primary Sjogren's syndrome presenting as hypokalemic paralysis: A case series

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## ABSTRACT

Primary Sjögren's syndrome (pSS) primarily involves exocrine glands, and renal tubular acidosis (RTA) is seen in one-third of the cases. RTA with hypokalemic paralysis as a presenting feature of pSS is described in few case reports in literature. We report 13 cases who presented as hypokalemic paralysis, and on evaluation were diagnosed to be pSS, as per the diagnostic criteria laid by the Sjögren's International Collaborative Clinical Alliance (2012). All patients were female, with a mean age at presentation being  $33.1 \pm 8.22$  years (range, 25–48 years). Eleven patients had a complete distal RTA and two patients had incomplete distal RTA at the time of presentation. 62% (8/13) of patients had no signs and symptoms of exocrine gland involvement. All the cases were managed with oral alkali therapy, and six patients received additional immunomodulating agents. No improvement in renal tubular dysfunction (in the form of a reduction in the alkali dose) after immunomodulating therapy was observed over a mean follow-up of 2.8 years. Renal tubular dysfunction can be the presenting manifestation of pSS. It is important to consider the possible presence of this disorder in adults with otherwise unexplained distal RTA or hypokalemia.

**KEY WORDS:** Anti-Ro/La, potassium citrate, renal tubular acidosis, Sjögren's International Collaborative Clinical Alliance 2012

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## Introduction

Hypokalemic paralysis is caused by a number of underlying etiologies, namely, genetic, endocrine, gastrointestinal, and renal.<sup>[1]</sup> Renal tubular acidosis (RTA) and thyrotoxicosis constitute the major causes of acquired hypokalemic paralysis. Distal RTA is the common pathway for potassium loss in a variety of diseases including connective tissue diseases such as Sjogren's syndrome (SS).

SS is a chronic autoimmune inflammatory disease with an estimated prevalence ranging from 0.1% to 4.8%, affecting mainly middle-aged females and primarily involves the exocrine glands.<sup>[2]</sup> The syndrome can present either alone (primary SS [pSS]) or in the context of an underlying connective tissue disease (secondary SS).<sup>[3]</sup> The prevalence of renal involvement in pSS ranges from

18.45% to 67%.<sup>[4]</sup> RTA with hypokalemic paralysis as a presenting feature of pSS is described in few case reports in literature. We present here a case series of 13 patients of pSS presenting as hypokalemic paralysis and review the related literature.

## Case Series

A single-center, retrospective data analysis of pSS cases presenting as hypokalemic paralysis due to RTA from January 2010 to December 2014. The study was approved by the Institutional Ethics Committee. Patients satisfying at least two of the following diagnostic criteria for SS by the Sjögren's International Collaborative Clinical Alliance (SICCA 2012)<sup>[5]</sup> were included in the study.

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1. Positive serum anti-SSA (Ro) and/or anti-SSB (La)
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score  $>1$  focus/4 mm
3. Keratoconjunctivitis sicca with ocular staining score  $>3$ .

Patients of hypokalemic paralysis with elevated spot urinary potassium-creatinine ratio ( $>13$  mEq/g) underwent blood gas analysis with simultaneous urine pH to establish the diagnosis of RTA. Patients with absent metabolic acidosis were subjected to acid load test with ammonium chloride. Ammonium chloride (100 mg/kg body weight) was given orally with lime juice. Urine pH and blood gas analysis was done on an hourly basis. Urine pH  $>5.5$ , after fall of blood bicarbonate ( $\text{HCO}_3^-$ )  $>3$  mEq/L from baseline, was considered as positive.

Patients were classified as follows:

- Complete distal RTA: Patients with normal plasma anion gap metabolic acidosis with urine pH  $>5.5$
- Incomplete distal RTA: Diagnosed in the absence of systemic acidosis with persistent urine pH  $>5.5$  on ammonium chloride load
- Proximal RTA: Patients with normal plasma anion gap metabolic acidosis with urine pH  $<5.5$ .

Serum antithyroid peroxidase antibodies, antithyroglobulin antibodies, anti-Ro/La antibodies, and other antinuclear antibodies quantitative estimation were done after the diagnosis of RTA was confirmed. Patients with positive anti-Ro/La antibodies were further subjected to lip biopsy for minor salivary gland inflammation and Schirmer's test. Schirmer's test  $<5$  mm at the end of 5 min was taken as positive.

All patients with distal RTA were treated with 1–3 mEq/kg of potassium citrate solution (1 ml = 2 mEq/L of  $\text{HCO}_3^-$  and 2 mEq/L potassium). The dose was titrated to maintain serum  $\text{HCO}_3^-$  levels between 22 and 24 mEq/L. Patients with extraglandular manifestation (namely, arthritis, arthralgia, and vasculitis) were treated with immunomodulating therapies such as oral hydroxychloroquine (HCQ) (200 mg BD) and methotrexate (7.5 mg to 15 mg weekly). No biological therapies were given to patients.

Forty-two patients of hypokalemic paralysis patients were referred to the Endocrine Department for the evaluation of the etiology. On further evaluation, 21 (50%) patients had RTA. All RTA patients were evaluated with antibody testing for connective tissue disorder and 13 patients satisfied the criteria for the diagnosis of pSS. All patients were female, with a mean age at presentation being  $33.1 \pm 8.22$  years (range, 25–48) and the mean duration of the disease being  $2.6 \pm 2.5$  years (range, 0–7). Eleven patients had a complete distal RTA and two patients had incomplete distal RTA (case 4 and 13) at the time of presentation. Both these patients had elevated spot urinary potassium-creatinine ratio ( $>13$  mEq/g). Only five patients had sicca symptoms at the time of presentation. Sixty-three percent (8/13) of patients had no signs and symptoms of exocrine gland involvement and were diagnosed to be SS after serology testing. All patients were tested positive

for anti-Ro and La antibodies, and other antinuclear antibodies were negative. Histopathology of lip biopsy showed minor salivary gland inflammation in all patients. Schirmer's test was positive ( $<5$  mm) in two patients (5 and 10). The detailed biochemical and serological characteristics of all the patients are given in Table 1.

Average alkali requirement per patient was 60–90 mEq of  $\text{HCO}_3^-$ /day. Five patients received oral HCQ and one patient received HCQ plus methotrexate for extraglandular manifestation. Eleven patients are actively following with us, with a mean duration of 2.8 years (range, 0.5–4). Long-term follow-up ( $>3$  years) was available for three patients (two patients on HCQ and one patient on HCQ and methotrexate); however, no improvement in the RTA was noticed in the form of a reduction in  $\text{HCO}_3^-$  and/or potassium requirements.

## Discussion

To the best of our knowledge, this is the largest case series of pSS presenting as hypokalemic paralysis. All patients were referred to rule out endocrine causes of hypokalemia. On evaluation, they were found to have pSS with RTA. Eleven patients had a complete distal RTA and two patients had incomplete distal RTA at the time of presentation. In all patients, the diagnosis of pSS was made after the onset of hypokalemic paralysis. Only 38% patients had sicca symptoms at the time of presentation.

The mean age of presentation ( $33.1 \pm 8.22$ ) in our patient was slightly younger compared to the age of presentation of pSS in general population (52.7 years).<sup>[6]</sup> The younger age at presentation may indicate that the renal involvement may set in before the onset of the other manifestations of the pSS. This finding needs further confirmation in a larger population of patients.

In the present study, pSS was diagnosed according to the SICCA 2012 classification which includes involvement of at least two clinical specialties and is based entirely on objective tests. Although the involvement of minor salivary gland was present in all patients at the time of presentation, 62% of the patients lacked clinical signs and symptoms of salivary gland involvement. A prospective study<sup>[7]</sup> showed that RTA is a common feature of SS. In the same study, it was implicated that pSS as a cause of RTA may be missed if the oral and ocular symptoms are absent at presentation.

The presence of renal involvement in SS has been known since the 1960s. Tubulointerstitial nephritis leading to tubular dysfunction is the most common underlying etiology.<sup>[8]</sup> Distal RTA is a common manifestation of tubulopathy, followed by nephrogenic diabetes insipidus and proximal RTA. The mechanism of distal RTA in SS is incompletely understood. Several case reports with immunocytochemical analysis on renal biopsy showed a complete absence of the H-ATPase pump in the intercalated cells of the collecting tubules that is largely responsible for distal proton secretion.<sup>[9,10]</sup> How the

**Table 1: Clinical and biochemical characteristics of cohort I**

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13
Age	33	45	22	36	25	42	42	26	25	35	23	27	48
Number of episodes	5	2	1	1	2	1	1	2	4	2	2	3	2
Sicca symptoms	Yes	No	No	No	Yes	Yes	No	Yes	No	No	No	No	Yes
Lip biopsy	+	+	+	+	+	+	+	+	+	+	+	+	+
Anti-Ro/La	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+
pH	7.28	7.2	7.3	7.37	7.29	7.1	7.318	7.16	7.32	7.1	7.1	7.3	7.42
HCO <sub>3</sub> (mEq/L)	14.2	14.2	12.9	24	13.4	11	18	11	15	12.8	14.5	8.6	21
Serum AG	5.6	3.8	11.1	8	10.6	7	9.5	12	10.5	4.2	11	12	6.5
Serum calcium/serum phosphorus (mg/dl)	8.2/2.17	7.5/2.4	8.3/2	9.8/4.7	9.8/3.78	9.1/2.77	7.3/1.8	7.2/2.2	7.2/2.8	9.1/1.9	7.7/2.1	8.2/3.5	8.5/3.5
Serum sodium/serum potassium (mEq/L)	140/2.5	142/1.7	137/1	139/1.3	135/2.6	136/1.2	143/1.3	140/1.6	139/1.4	145/2.7	139/2.9	140/2.5	136/1.2
Urine pH	6.8	7.6	7	5.8	6.57	7	6.5	7	7.5	8	7	7.2	7.2
Urine AG	35	21	26	6.5	18	16	35.6	29	12	16.3	8	1	4.5
Glucosuria	-	-	-	-	-	-	-	-	-	-	-	-	-
Proteinuria	-	-	-	+	-	-	-	-	-	-	-	-	+
Urine calcium creatinine ratio	0.52	0.38	0.14	0.38	0.1	0.4	0.41	0.11	0.21	0.78	0.11	NA	0.21
Nephrocalcinosis	+	-	-	-	-	-	-	-	-	+	-	-	-

AG: Anion gap, NA: Not available, HCO<sub>3</sub>: Bicarbonate

immune injury leads to loss of H-ATPase activity is not known. Autoantibody directed against carbonic anhydrase II has been proposed as another mechanism of distal RTA in pSS.<sup>[11]</sup>

RTA *per se* is not a usual indication for the immunomodulating therapy in pSS. Theoretically, RTA with pSS may merit immunomodulating therapy as RTA, it can be considered as another extraglandular manifestation based on its prevalence (up to 67%)<sup>[4]</sup> and similar histologic findings in salivary glands and kidneys. It is, therefore, conceivable that the RTA in SS is an inherent manifestation.<sup>[12,13]</sup> We have restricted the use of immunomodulating therapy for patients with classical extraglandular manifestations. Six patients received immunomodulating therapy, but no improvement in the RTA was noticed. Biological agents were not used in our patients, and in literature also, the effect of biological agents on renal manifestation is not available.

The limitations of this study are a small number of patients and retrospective study design. We have not performed a kidney biopsy to know the type of tubular involvement and response to immunosuppressive therapy. The use of immunocytological staining on renal biopsy and identification of antigenic targets of autoimmunity in renal tubule may be helpful in the diagnosis and better management of the disease in the future.

### Conclusion

The present study and review of literature showed that the renal tubular dysfunction can be the presenting manifestation of pSS. It is important to consider the possible presence of this disorder in any adult with otherwise unexplained distal RTA.

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### Conflicts of interest

There are no conflicts of interest.

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