Rheumatology International (2018) 38:2251–2262
https://doi.org/10.1007/s00296-018-4118-x

Rheumatology
INTERNATIONAL

COHORT STUDIES

# Renal involvement in primary Sjogren's syndrome: a prospective cohort study

**Ankit Jain[1,4] · Bheemanathi Hanuman Srinivas[2] · Dantis Emmanuel[1,5] · Vikramraj K. Jain[1,6] · Sreejith Parameshwaran[3] · Vir Singh Negi[1]**

Received: 31 May 2018 / Accepted: 2 August 2018 / Published online: 23 August 2018


## Abstract

The objective of the study is to prospectively evaluate the spectrum of clinical and subclinical renal involvement in patients with primary Sjogren's syndrome (pSS). Of the 174 patients screened, seventy patients with pSS underwent renal function tests, urine examination, renal ultrasound, arterial blood gases, urine pH followed by urine acidification test and renal biopsy (if indicated). Renal tubular acidosis (RTA) was treated with alkali replacement and moderate–severe tubulointerstitial nephritis (TIN) was treated with oral prednisolone. Sixty-two patients completed 1-year follow-up. A comparison was made between patients with and without renal involvement. Thirty-five (50%) patients had renal involvement. They had a lower baseline eGFR ($71.85 \pm 18.04$ vs. $83.8 \pm 17$, $p = 0.005$). Twenty-nine patients had RTA (25 complete and 4 incomplete). Eleven patients had urinary abnormalities. Patients with RTA ($n = 29$) were younger ($34.9 \pm 9$ vs. $42 \pm 11.3$, $p = 0.006$), had fewer articular (34% vs. 78%, $p = 0.001$) and ocular sicca (62% vs. 88%, $P = 0.01$) than those without RTA ($n = 41$) and commonly presented with hypokalemic paralysis. On biopsy, TIN (9/17) and IgA nephropathy (3/17) were most common. On follow-up, there was no clinically significant change in eGFR; however, one patient with renal calculi and incomplete distal renal tubular acidosis (dRTA) progressed to complete dRTA. Two patients treated with steroids had marginal improvement in eGFR. Renal involvement in pSS is under-recognized with the most common manifestation being RTA presenting with hypokalemic paralysis. These patients are younger with less articular and sicca symptoms. Subclinical RTA may progress to complete RTA. Renal biopsy should be considered in all patients with renal involvement.

**Keywords** Primary Sjogren's syndrome · Tubulointerstitial nephritis · Sicca · Renal tubular acidosis · Renal biopsy · Hypokalemic paralysis

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00296-018-4118-x) contains supplementary material, which is available to authorized users.

✉ Vir Singh Negi
vsnegi22@yahoo.co.in; negi.v@jipmer.edu.in

Ankit Jain
ankit83jain@gmail.com

Bheemanathi Hanuman Srinivas
Srinivas.bh08@gmail.com

Dantis Emmanuel
drdantis@gmail.com

Vikramraj K. Jain
vikramraj.jain@gmail.com

Sreejith Parameshwaran
sparameswaran@outlook.com

[1] Department of Clinical Immunology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India

[2] Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India

[3] Department of Nephrology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India

[4] Present Address: Immunology and Rheumatology Clinic, Meerut, UP 250001, India

[5] Present Address: Rajagiri Hospital, Chunangamvely, Aluva, Kerala 683112, India

[6] Present Address: Bhagwan Mahavir Jain Hospital, Bangalore, India

**Abbreviations**

| | |
|---|---|
| pSS | Primary Sjogren's syndrome |
| RTA | Renal tubular acidosis |
| TIN | Tubulointerstitial nephritis |
| eGRF | Estimated glomerular filtration rate |
| dRTA | Distal renal tubular acidosis |
| GN | Glomerulonephritis |
| IN | Interstitial nephritis |
| iRTA | Incomplete distal renal tubular acidosis |
| AECG | American–European consensus group |
| ANA | Antinuclear antibody |
| ELISA | Enzyme-linked immunosorbent assay |
| RF | Rheumatoid factor |
| ABG | Arterial blood gases |
| UAT | Urine acidification test |
| cRTA | Complete distal renal tubular acidosis |
| ESSDAI | EULAR Sjögren's Syndrome Disease Activity Index |
| NSAID | Non-steroidal anti-inflammatory drugs |
| IFTA | Moderate interstitial fibrosis and tubular atrophy |
| FSGS | Focal segmental glomerulosclerosis |
| ATN | Acute tubular necrosis |
| NLR | Neutrophil/lymphocyte ratio |
| NCCT | NaCl cotransporter |
| CA | Carbonic anhydrase |
| CIN | Chronic interstitial nephritis |
| TLR | Toll-like receptors |
| SPSS | Statistical package for the social sciences |
| SS-A | Sjogren's syndrome-related antigen A |
| SS-B | Sjogren's syndrome-related antigen B |

## Introduction

Primary Sjögren's syndrome (pSS) is a common autoimmune disease with an enormous impact on the quality of life. The most characteristic manifestation is sicca syndrome secondary to infiltration of exocrine glands by lymphocytes. Besides, extra-glandular manifestations may be seen in almost three-quarters of patients which sometimes may be life threatening.

The prevalence of renal involvement in pSS varies from 1 to 33% depending on the population studied, criteria used for diagnosis and nature of the study [1–4]. Renal manifestations can be heterogeneous, varying from mild electrolyte abnormalities to complete distal renal tubular acidosis (cRTA), interstitial nephritis (IN) or glomerulonephritis (GN) [5]. If left untreated, these may lead to serious consequences. Incomplete dRTA (iRTA) demonstrated by abnormal acidification of urine without overt acidosis may also be seen in almost 1/3rd of the patients with pSS [6–8]. Though it has been shown to be associated with the formation of renal calculi, the exact natural history of such patients has never been evaluated.

Studies in various Western and Chinese pSS cohorts suggest that tubulointerstitial nephritis (TIN) is the most common manifestation followed by GN which is commonly associated with cryoglobulinemia [5]. However, there is a paucity of such data from the Indian subcontinent. More so, there is no clarity regarding the role of renal biopsy and immunosuppressive therapy in pSS patients with renal involvement though recent retrospective studies seem to suggest that immunosuppression with corticosteroids and other immunosuppressive agents may retard the progression of renal disease [9–11].

Hence, we conducted this prospective cohort study to investigate the spectrum of clinical and subclinical renal involvement in patients with pSS. The patients were followed up for a period of 1 year for evolution of renal disease and response to therapy.

## Methods

### Study design

This was a prospective cohort study wherein patients were followed up for 1 year. This study was conducted over 2 years (2015–2016) at the department of Clinical Immunology of a tertiary care hospital in southern India.

### Patient population

All patients with signs and symptoms suggestive of pSS, attending the outpatient clinic of our department and those referred from inpatient wards of medicine and nephrology, were screened. Inclusion criteria were patients $\geq 18$ years age satisfying the 2002 AECG (American–European consensus group) criteria for diagnosis of pSS [12]. Exclusion criteria were presence of anatomical renal defects, essential hypertension, diabetes mellitus, drug-induced renal disease, malignancy of the genito-urinary tract, and pregnancy or breast feeding.

### Study protocol

Clinical features of all study subjects were documented. Relevant immunological investigations including antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) on Hep2 cells, anti-SSA/SSB antibodies by quantitative ELISA and IgM rheumatoid factor (Classic RF), C3 and C4 levels by nephelometry, etc., were done. Assessment of renal involvement included renal function tests, serum electrolytes, arterial blood gases (ABG), urine r/m, urine protein estimation, urine pH, X-ray, and renal ultrasound.

Patients found to have normal blood pH and morning urine pH > 5.5 underwent a urine acidification test (UAT) [13]. UAT in eligible patients was done by administering a single dose of tablet furosemide (40 mg) and fludrocortisone (1 mg) orally, after collecting the baseline urine sample. Fluid intake was allowed to be ad libitum. Urine was collected hourly for 6 h after drug ingestion and urine pH measured immediately. Inability to decrease urinary pH to < 5.3 in 6 h was considered to be due to the presence of subclinical dRTA. Patients were monitored for development of hypertension during the test. Renal biopsy was performed in patients with active urinary sediments, proteinuria > 500 mg/day, renal dysfunction or active renal tubular acidosis.

Renal involvement was defined as one or more of the following [14, 15]:

1. Complete distal RTA (cRTA),
2. Positive urine acidification test without overt acidosis with or without hypokalemia (incomplete dRTA, iRTA),
3. Renal colic with findings of nephrolithiasis or nephrocalcinosis and overt dRTA or positive UAT,
4. Fanconi's syndrome not associated with any known cause,
5. Reduced creatinine clearance (< 60 ml/min, CKD-EPI),
6. Proteinuria > 500 mg/24 h,
7. Active urinary sediments and
8. Renal biopsy demonstrating histological features compatible with GN, interstitial nephritis, or both.

### Treatment and follow-up

All patients were treated with hydroxychloroquine 4–6 mg/kg body weight (maximum 400 mg/day) unless contraindicated. Renal tubular acidosis was treated with alkali replacement. Patients with moderate to severe TIN were treated with 1 mg/kg prednisolone tapered over 3–6 months. Glomerulonephritis was to be treated according to renal histology.

All the patients were screened for development of new onset renal involvement every 12 weeks for 1 year. Disease activity was assessed by ESSDAI (EULAR Sjögren's syndrome Disease Activity Index) and renal dysfunction by eGFR (CKD-EPI, ml/min) at baseline, 6 months and at 12 months. At the end of 1 year, patients were stratified into two groups: renal group, comprising patients with renal involvement and non-renal group comprising patients without renal involvement.

Clinical and immunological profiles of the two groups were compared along with change in ESSDAI and mean eGFR at 12 months.

### Statistical analysis

Sample size was estimated using OpenEpi software (version 3.01 software) for estimating a proportion with 25% relative precision and 95% confidence interval. The expected prevalence of renal involvement was 38%, and the sample size estimated for the study was 100. However, enrollment was stopped at 70 because of time constraints. Normality of data distribution was assessed by Kolmogorov–Smirnov. Normally distributed data were presented as mean ± SD. The non-normal distributed data were represented as median (min–max). Groups were compared using Chi-square or Fischer's exact test for categorical variables and using independent Student's *t* test/Mann–Whitney *U* test for continuous data. Change in parameters over 1 year was compared by paired *t* test/Wilcoxon signed rank sum test using imputation analysis. A *p* value of < 0.05 was considered as significant. Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago) for windows.

### Ethical approval

The study protocol was approved by the institutional ethics committee, and all the study subjectsprovided written informed consent.

## Results

A total of 178 subjects with suspected pSS were screened during the study period, and 84 patients satisfying the AECG 2002 criteria for pSS were considered for the study. Of these, 14 patients were excluded (Fig. 1) and remaining 70 were included. Thirty-five (50%) patients were found to have renal involvement (renal group). Sixty-two patients completed 12-month follow-up (Fig. 1).

### Demography (Table 1)

The mean age ± SD of the cohort was 39.1 ± 10.9 years, and 68 were females. Thirty-five (50%) patients had renal involvement (renal group) and 35 (50%) were not having renal involvement (non-renal group). All patients in the renal group and 33 in the non-renal group were females. There was no significant difference between the renal and non-renal group with respect to the age of onset of pSS, age at enrollment, age at diagnosis, disease duration* and delay in diagnosis*.

### Clinical and glandular manifestations (Table 1)

Ocular sicca (23/35) and articular manifestations (14/35) were less common while parotid swelling was more common

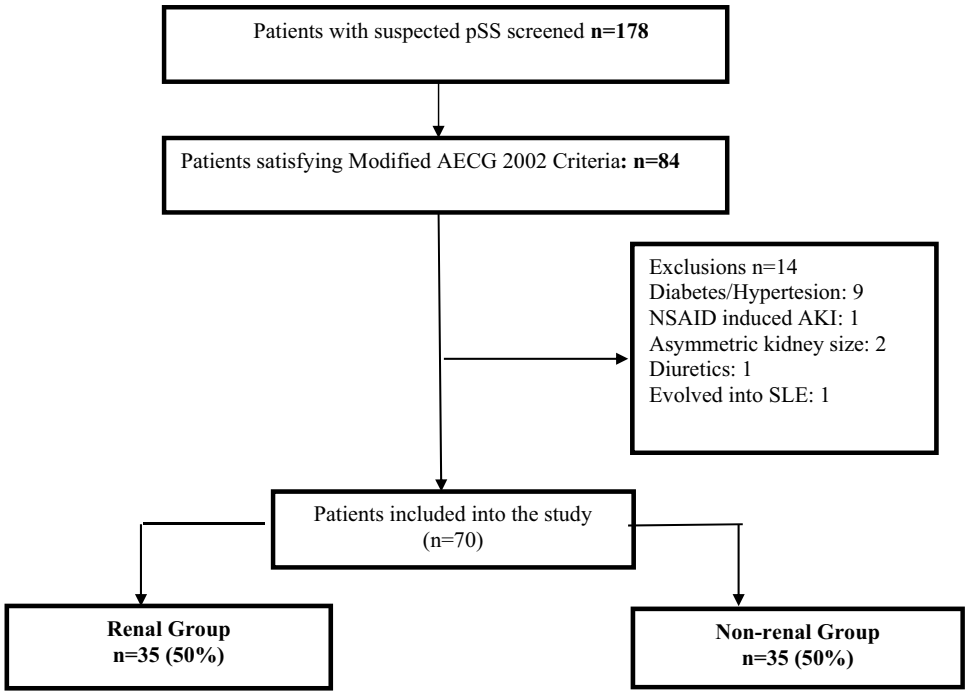


**Fig. 1** Study flowchart

(13/35) in the renal group compared to the non-renal group. There was a trend toward higher cutaneous vasculitis (10/35) in the renal group though the result was not statistically significant. There was no significant difference between the two groups with respect to the other manifestations including interstitial lung disease*, leucopenia*, neurological manifestations*, parotitis* and hypothyroidism*. The mean baseline eGFR (CKD-EPI, ml/min) was lower ($p = 0.005$), and the median baseline ESSDAI in the renal group was higher ($p < 0.001$) in the renal group as compared to the non-renal group.

*Data not shown.

## Immunological profile (Table 1)

There was no statistically significant difference in the immunological profile between the two groups. Anti-SSA/SSB antibodies and hypergammaglobulinemia were more common in renal group though the difference was not statistically significant.

## Renal involvement (Fig. 2)

Twenty-five of 35 patients had cRTA and 4/35 had iRTA. The most common clinical manifestation was hypokalemic paralysis (19/35). Besides, nephrocalcinosis and metabolic bone disease was also seen. None of the patients had proximal RTA. Overall, 6/70 patients had a history of renal calculi. Two of them had cRTA. The third patient initially had mild renal dysfunction and iRTA which progressed to cRTA with hypokalemia and frank metabolic acidosis at 9th month of follow-up. All the three were included in the renal group. Rest of the three patients with calculi had a negative UAT and were included in the non-renal group. Renal dysfunction and urinary abnormalities were seen in 11/70 (16%) patients.

## Treatment profile

The treatment that the patients had received at any point of their disease was compared between the two groups. There was no difference between the two groups with respect to the use of immunomodulator and immunosuppressive drugs. NSAID intake was also similar between the two groups. All patients with cRTA were treated with alkali replacement including the patient with iRTA, who developed cRTA at 9th month. Of the four patients with moderate TIN, two gave their consent for treatment with prednisolone.

*Renal biopsy* (Fig. 3) Of the total of 35 patients with renal involvement, renal biopsy could only be performed for 17 patients, all of whom had dRTA. Three of those seventeen had pyuria, two had proteinuria and three had renal dysfunction. Twelve patients had normal urine examination of whom nine had abnormal renal biopsy. The most common finding on histopathology was TIN 9 (52.9%) showing patchy or diffuse interstitial inflammation. Glomerular changes were present in 6/17 patients. Three/seventeen had early IgA nephropathy with mild-mod TIN, and two (11.7%) had a mild mesangial expansion with mild-mod TIN. Two patients with history of renal calculi had moderate interstitial fibrosis and tubular atrophy (IFTA). One of them additionally

**Table 1** Baseline features

| Variable | Renal ($n=35$) | Non-renal ($n=35$) | *P* Value | OR | 95% CI |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Female:male | All females | 33:2 | – | – | – |
| Age[a], Y | 37.6 ± 11 | 40.6 ± 10.7 | 0.24[£] | – | −8.2 to (2.16) |
| Age of onset[a], Y | 32 ± 12.5 | 34 ± 13.1 | 0.55[£] | – | −7.9 to (4.29) |
| Age at diagnosis[a], Y | 35.6 ± 11.3 | 39.4 ± 10.6 | 0.14[£] | – | −9.1 to (1.3) |
| Clinical and glandular features | | | | | |
| Oral sicca, *n* (%) | 32 (91) | 33 (94) | 0.21[ƨ] | 0.6 | 0.1 to 4.1 |
| Ocular sicca, *n* (%) | 23 (66) | 31 (89) | 0.02[#,ƨ] | 0.1 | 0.7 to 0.9 |
| Parotid swelling, *n* (%) | 13 (37) | 4 (11) | 0.01[#,ƨ] | 4.5 | 1.3 to 15.9 |
| + Sal. Scint.[d], *n* (%) | 26/30 (87) | 24/34 (71) | 0.1[ƨ] | 0.4 | 0.1 to 1.3 |
| + Schirmer's test[d], *n* (%) | 9/33 (27) | 12/34 (35) | 0.5[ƨ] | 1.4 | 0.5 to 4.1 |
| Ocular staining score[d] | 10/27 (37) | 8/26 (30) | 0.8[ƨ] | 0.7 | 0.2 to 2.3 |
| MSGB[d] positive, *n* (%) | 22/28 (79) | 24/33 (73) | 0.3[ƨ] | 0.7 | 0.2 to 2.3 |
| Articular *n* (%) | 14 (40) | 28 (80) | 0.001[#,ƨ] | 0.2 | 0.06 to 0.49 |
| Cut. Vasc. *n* (%) | 10 (29) | 4 (11) | 0.07[ƨ] | 3.1 | 0.9 to 11.1 |
| Mean eGFR[b] | 71.85 ± 18.04 | 83.8 ± 17 | 0.005[#,£] | – | −20.3 to (−3.6) |
| ESSDAI | 6 (2–10) | 2 (1–4) | < 0.001[€#] | – | – |
| NSAID intake, *n* (%) | 17 (49) | 24 (69) | 0.09[ƨ] | 0.4 | 0.2 to 1.1 |
| Immunological profile | | | | | |
| ANA+, *n* (%) | 35 (100) | 33 (94) | 0.49[ƨ] | 1.1 | 0.9 to 1.1 |
| RF+, *n* (%) | 29 (83) | 26 (74) | 0.38[ƨ] | 1.7 | 0.5 to 5.3 |
| Anti-SSA+, *n* (%) | 34 (97) | 28 (80) | 0.06[ƨ] | 8.5 | 0.99 to 73 |
| Anti-SSB+, *n* (%) | 25 (71) | 18 (51) | 0.08[ƨ] | 2.3 | 0.9 to 6.3 |
| Low C3/C4 *n* (%) | 7 (20) | 9 (26) | 0.56[ƨ] | 0.7 | 0.2 to 2.2 |
| IgG levels, (g/l)[c,d] | 21.5 (8.2–40.5)/31 | 18.7 (7.2–64.6)/35 | 0.32[€] | – | – |

*Y* years, *Sal. Scint.*: salivary scintigraphy, *IQR* interquartile range, *OR* odds ratio, *CI* confidence interval, *MSGB* minor salivary gland Biopsy, *Cut. Vasc* cutaneous vasculitis, *NLR* neutrophil lymphocyte ratio, *ANA* antinuclear antibody, *RF* rheumatoid factor

[a]Mean ± standard deviation

[b]ml/min, CKD-EPI

[c]Median (min–max)

[d]Missing values

[#]Significant *p* value < 0.05

[€]Compared using non-parametric test Mann–Whitney test

[ƨ]$\chi^2$ test used

[£]Student's test

had focal segmental glomerulosclerosis (FSGS) also. Mild acute tubular necrosis (ATN) was present in 2/17 patients and mild-mod TIN in 4/17. Renal biopsy was normal in 4/17 patients of which one had pyuria and one had renal dysfunction. The details of the patients who underwent renal biopsy are provided in Table 2.

*Follow-up* (Table S1) At 12 months, a statistically significant improvement in the mean eGFR from baseline was observed in the renal group [−6.05 ± 10.9, $P=0.002$]. However, the change was not significant in the non-renal group (4.62 ± 14.3, $P=0.6$). There was a significant reduction in median ESSDAI in the renal group compared to the non-renal group [5(0–6) vs. 0(0–2), $p=0.001$]. However, the change in neutrophil/lymphocyte ratio (NLR) was non-significant for the two groups. In patients with complete dRTA ($n=25$), there was a significant improvement in blood pH, $HCO3^-$ and serum potassium from baseline at 12 months with alkali replacement: blood pH [7.32 ± 0.09 vs. 7.37 ± 0.04, $p=0.001$], $HCO3^-$ (mmol/L) [15.9 ± 4.3 vs. 18.9 ± 2.8, $p=0.005$] and serum potassium (mEq/L) [3.38 ± 0.9 vs. 3.9 ± 0.5, $p=0.005$], respectively. For the patient who developed cRTA during follow-up at 9 months, alkali replacement corrected her acidosis and hypokalemia and she had not developed any episode of hypokalemic paralysis over next 6 months till the time of writing of this manuscript.

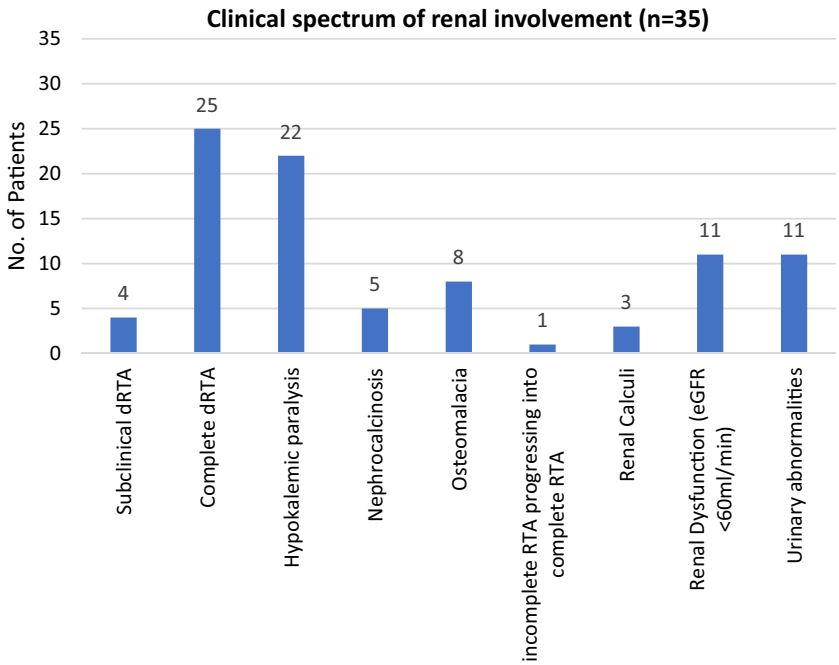


**Fig. 2** Clinical spectrum of renal involvement. *dRTA* distal renal tubular acidosis, *iRTA* incomplete RTA

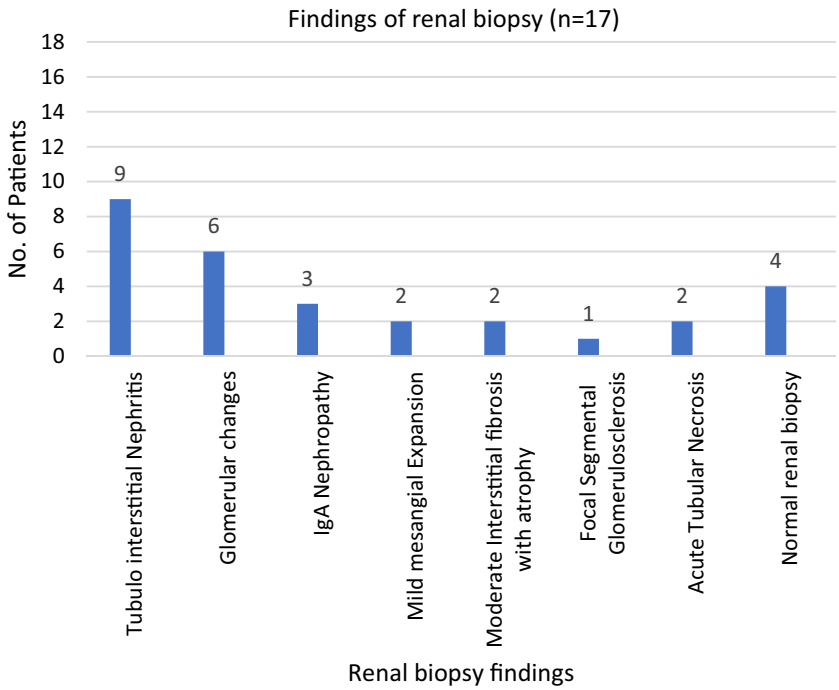


**Fig. 3** Renal biopsy

## Response to steroid treatment

Four patients had RTA with moderate TIN. After taking informed consent, two patients were treated with prednisolone. There was a mild clinically insignificant improvement in eGFR in both the patients with treatment (5 and 8 ml/min, respectively). However, there was no change in the alkali requirement in one patient, and there was a mild reduction of 20 mEq in the other patient.

## Subgroup analysis (RTA vs non-RTA)

The mean age, the age of onset and the age at diagnosis in patients with RTA were significantly lower than those without RTA (Table 3.) Patients with RTA had less of ocular

**Table 2** Profile of patients who underwent renal biopsies

| P. no. | Age (Y) | Ds Dur (M) | Renal manifestation | Dry eye | Dry mouth | Urine | I/C for biopsy | eGFR | ANA | RF | Low C3/C4 | SSA | SSB | Biopsy finding | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 32 | 120 | RTA, HP | + | + | N | RTA | 61 | + | + | − | + | + | N | A |
| 2 | 30 | 84 | RTA, RD | + | − | N | RD | 51 | + | + | − | + | − | N | A |
| 3 | 24 | 24 | RTA, HP, OM | − | + | N | RTA | 63 | + | + | − | + | − | Mild mesangial expansion + mod TIN | A |
| 4 | 52 | 120 | RTA, HP, OM | − | + | N | RTA | 75 | + | + | + | − | + | Early IGAN + mild TIN | A |
| 5 | 20 | 84 | RTA, HP, NC | + | + | N | RTA | 72 | + | + | + | + | + | Mild TIN | A |
| 6 | 50 | 72 | RTA, HP, OM | + | + | P | RTA + P | 61 | + | + | − | + | − | Mild ATN | A |
| 7 | 38 | 72 | RTA, RC, RD, H, NC, OM | + | − | N | RTA, RD | 58 | + | + | − | + | + | FSGS + mod IFTA | A |
| 8 | 40 | 48 | RTA, HP, OM | + | − | Py | RTA, Py | 63 | + | − | − | + | + | N | A |
| 9 | 33 | 120 | RC, RD iRTA◊ cRTA | + | + | N | RTA, RD | 51 | + | + | − | + | + | mod IFTA | A |
| 10 | 28 | 12 | RTA, HP | + | − | N | RTA | 68 | + | + | + | + | − | N | A |
| 11 | 42 | 36 | RTA, HP | + | − | Py | RTA, Py | 56 | + | + | + | + | + | Mod TIN | A + S |
| 12 | 29 | 1 | RTA, HP | + | + | N | RTA | 76 | + | + | − | + | + | Mild TIN | A |
| 13 | 24 | 72 | RTA, HP, OM, NC | + | − | Py | RTA, Py | 79 | + | + | − | + | + | Early IGAN + mild TIN | A |
| 14 | 28 | 72 | RTA, HP | + | + | P | RTA, P | 64 | + | + | + | + | − | Mild mesangial expansion + TIN | A |
| 15 | 32 | 24 | RTA, HP | + | − | N | RTA | 66 | + | + | − | + | + | Mild ATN | A |
| 16 | 23 | 20 | RTA, HP | + | − | N | RTA | 90 | + | − | − | + | + | Mod TIN | A + S |
| 17 | 45 | 2 | RTA, HP | + | + | N | RTA | 68 | + | − | − | + | + | Early IGAN + mod TIN | A |

*RD* renal dysfunction, *HP* hypokalemic paralysis, *OM* osteomalacia, *NC* nephrocalcinosis, *RTA* renal tubular acidosis, *iRTA* incomplete RTA, *cRTA* complete RTA, *H* hypokalemia, *RC* renal calculi, *TIN* tubulointerstitial nephritis, *FSGS* focal segmental glomerulosclerosis, *ATN* acute tubular necrosis, *IFTA* interstitial fibrosis and tubular atrophy, *S* steroids, *A* alkali replacement, *P* proteinuria, *Py* pyuria, *N* normal

**Table 3** Subgroup analysis: RTA vs. Non-RTA

| Clinical feature | RTA $n=29$ | Non-RTS $n=41$ | *P* value | OR | 95% CI |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Female:male | All females | 39:2 | – | – | – |
| Age[a], years | 34.9 ± 9 | 42 ± 11.3 | 0.006[£#] | – | − 12.1 to (− 2.0) |
| Age of onset[a], Years | 29.3 ± 10 | 35.8 ± 13.8 | 0.03[£#] | – | − 12.5 to (− 0.5) |
| Age at diagnosis[a], years | 32.8 ± 9.1 | 40.8 ± 11.3 | 0.002[£#] | – | − 13 to (− 2.9) |
| Clinical manifestations | | | | | |
| Oral sicca, *n* (%) | 26 (90) | 39 (95) | 0.38[ǂ] | 0.44 | 0.06 to 2.84 |
| Ocular sicca, *n* (%) | 18 (62) | 36 (88) | 0.012[ǂ#] | 0.23 | 0.07 to 0.75 |
| MSGB[b] positive, *n* (%) | 18/24 (75) | 28/37 (75) | 1.00[ǂ] | 0.96 | 0.29 to 3.1 |
| Articular, *n* (%) | 10 (34) | 32 (78) | 0.001[ǂ#] | 0.15 | 0.05 to 0.42 |
| Cutaneous vasculitis, *n* (%) | 9 (31) | 5 (12) | 0.052[ǂ] | 3.2 | 0.9 to 10.9 |
| NSAID intake, *n* (%) | 13 (45) | 28 (68) | 0.05[ǂ] | 0.57 | 0.33 to 1.0 |
| Immunological parameters | | | | | |
| ANA, *n* (%) | 29 (100) | 39 (95) | 0.22[∐] | 1.05 | 0.98 to 1.12 |
| RF +, *n* (%) | 24 (83) | 31 (76) | 0.47[ǂ] | 1.54 | 0.47 to 5.1 |
| Anti-SSA +, *n* (%) | 28 (97) | 34 (83) | 0.07[ǂ] | 5.8 | 0.66 to 49.6 |
| Anti-SSB +, *n* (%) | 21 (72) | 22 (54) | 0.11[ǂ] | 2.27 | 0.8 to 6.2 |
| Low C3/C4, *n* (%) | 6 (21) | 10 (24) | 0.7[ǂ] | 0.8 | 0.26 to 2.55 |

*M* months, *Sal. Scint*. salivary scintigraphy, *IQR* interquartile range, *OR* odds ratio, *CI* confidence interval, *RTA* renal tubular acidosis, *MSGB* minor salivary gland Biopsy, *ANA* antinuclear antibody, *RF* rheumatoid factor

[a]Mean ± standard deviation

[b]Missing value

[#]Significant *p* value < 0.05

[ǂ]$\chi^2$ test used

[£]Student's test

sicca ($p=0.005$) and articular manifestations ($p=0.001$). The groups did not differ with respect to other clinical and immunological profile. The most common presenting manifestations were hypokalemic paralysis [19(65%)] in the RTA group and articular [26(63%)] and sicca symptoms [10(24%)] in the non-RTA group.

## Discussion

We prospectively studied the renal manifestations in 70 patients with pSS. Half of these patients ($n=35$) had renal involvement mainly in the form cRTA ($n=25$) presenting commonly with hypokalemic paralysis and few ($n=4$) having incomplete RTA. Patients with renal involvement had fewer articular and sicca symptoms but cutaneous vasculitis and renal dysfunction were more prevalent. TIN was the most common histological lesion on renal biopsy. Additionally, mild glomerular changes were seen in a few of them. Clinically insignificant changes in renal function were observed during 12-month follow-up. Patients with dRTA were younger by almost 7 years at disease onset and presentation.

The prevalence of renal involvement in our study was higher than that seen in previous studies [6, 15–17]. The prospective follow-up design could have contributed to the higher prevalence considering the fact that most of the previous studies evaluating renal manifestations in pSS have been either retrospective or cross-sectional studies. However, a referral bias could not be ruled out since ours is a tertiary care hospital and patients diagnosed with RTA are actively screened for Sjogren's syndrome.

Our cohort was almost one decade younger as compared to Western cohorts, an observation which has been replicated in various Asian cohorts [3, 4]. Moreover, the mean age of the patients with renal involvement was also at least one decade lesser as compared to other western series [6, 15, 18] and was comparable to other Asian studies [19–21]. Possibly various environmental and predisposing genetic factors may be at play for an early onset of the disease which needs to be evaluated further. All patients with renal involvement were females. The two groups were not different with respect to age, a finding similar to a previous study [16].

The renal group had lesser ocular sicca symptoms. However, there was no statistically significant difference in oral sicca symptoms between the groups, probably because

patients with interstitial nephritis usually have tubular concentration defects and may falsely report polydipsia as sicca symptoms. Few studies have compared glandular manifestations between patients with and without renal involvement, and one such study found no difference [14, 15]. Literature suggests that only around 40% of patients with renal involvement have sicca symptoms [20, 21] and renal manifestations may precede the onset of sicca symptoms [16]. In our study, four patients with RTA had a normal renal histopathology, and interestingly, two of them did not have ocular sicca symptoms suggesting that other mechanisms besides lymphocytic infiltration of organs may be responsible for tubular dysfunction in these patients like antibodies against thiazide-sensitive NaCl cotransporter (NCCT), carbonic anhydrase (CA) or H + ATPase [22–27]. These antibodies were not evaluated in our patients, but it may be worthwhile to measure them in these patients.

Patients with renal involvement had less articular manifestations and more cutaneous vasculitis though the latter was not statistically significant probably because of small sample size. One study found a high prevalence of 77% of articular symptoms in pSS patients with renal involvement [15]. However, being a retrospective study, it had its own limitations. Despite extensive literature search, we were unable to find studies comparing extra-glandular manifestations in pSS patients with and without renal involvement. Hence, these findings need to be evaluated further in larger cohorts of patients.

Anti-SSA/SSB antibodies are known to be associated with extra-glandular manifestations [18]. However, their association with renal involvement is still unclear [7, 16, 28]. Many studies have suggested an association between hypergammaglobulinemia and RTA [7, 8, 28, 29]. But few studies in pSS suggested otherwise [30, 31]. In our study, the renal group had a higher prevalence of hypergammaglobulinemia and anti-SSA/SSB antibodies though the difference failed to reach statistical significance possibly due to the limited sample size. Our findings suggest a higher B cell activation in pSS patients with renal involvement, though the hypothesis merits further evaluation.

The most common renal manifestation was dRTA commonly manifesting as hypokalemic paralysis and osteomalacia. Barring one study [19], literature regarding metabolic bone disease in pSS patients with RTA is sparse. The prevalence of subclinical RTA in various cohorts has varied from 7 to 25% [3, 6, 7, 19]. Most of these studies have used the ammonium chloride loading (NH4Cl) test for evaluation of acidification defects. In our study, we used urine acidification test (UAT) by administering furosemide (40 mg) and fludrocortisone (1 mg) orally in patients having a urinary pH > 5.5 at baseline. UAT has been shown to be comparable to NH4Cl test for evaluation of iRTA in non pSS patients [13]. Considering the ease of conducting the test and minimum discomfort to the patients, UAT was employed in our study instead of the NH4Cl test. Though we found that the prevalence of iRTA using UAT was comparable to various pSS cohorts using NH4Cl, this test needs further validation in case of pSS especially in the light of new evidence which has questioned the utility of UAT in patients with pSS [6]. Renal dysfunction was present in almost 1/6th of our pSS cohort which was lesser as compared to other studies. However, these studies varied in their method of assessment of renal dysfunction [7, 28, 32].

The progression of one patient from iRTA to cRTA during follow-up and prevention from developing hypokalemic paralysis by alkali replacement highlight the need to screen patients with pSS for iRTA and follow them up for progression. Literature suggests that alkali replacement prevents the development of nephrolithiasis in patients with iRTA though this fact has not been evaluated formally in pSS patients [33, 34]. We propose that all patients with pSS should be screened for the iRTA. Those found to have iRTA should be followed up for the development of cRTA and be treated with alkali replacement. Role of alkali replacement in iRTA warrants further evaluation.

Retrospective studies suggest that interstitial nephritis in pSS may be associated with renal dysfunction [9, 11, 15]. We found that the mean baseline GFR was lower in the renal group. But surprisingly, there was a mild improvement in GFR at 12 months without specific treatment though the quantum of change was not clinically significant. Moreover, the long natural history of the disease precludes any definite inference to be drawn regarding progression of renal dysfunction over such a short duration. Prospective long-term studies may clarify the long-term impact of renal involvement in pSS.

Renal biopsy in pSS is an enigma. There are no clear-cut guidelines for renal biopsy in patients presenting with isolated tubular dysfunction. Studies show that without treatment, pSS patients with RTA and IN develop progressive renal dysfunction and interstitial fibrosis. This suggests a possible niche for renal biopsy in these patients [9, 11, 15]. We performed renal biopsy for all patients with RTA unless contraindicated. Similar to other studies, the most common histologic finding in our patients was TIN [7, 9, 15], which has been shown to be associated with loss of NCCT [27] and H+–ATPase in the collecting ducts leading to tubular dysfunction [22, 23, 35]. Two patients had IFTA without any cellular infiltration, of which one patient also had FSGS. Both these patients had renal calculi which are known to be associated with FSGS and CIN. In pSS, tubulointerstitial inflammation has been shown to promote interstitial fibrosis and development of CKD [5, 22, 27] Thus, whether stones or the disease itself caused the fibrosis might not be clear. Three patients had early IgA nephropathy and two had mild mesangial expansion both of which have been

well documented in the literature [7, 15, 16, 36]. None of our patients were found to have frank glomerulonephritis. This could be attributed to lack of cryoglobulins in any of our patients and a referral bias arising out of the fact that patients with glomerulonephritis presenting to other departments may not have been diagnosed as pSS.

Patients with RTA are usually treated with alkali replacement. Studies evaluating the role of immunosuppression in pSS patients with RTA and IN have shown either improvement or at least a stabilization of GFR [7, 9, 11, 15] though treatment with steroids was not shown to reduce alkali requirement [20]. In our patients, there was a marked improvement in acidosis with alkali replacement.

In the two patients treated with steroids, marginal improvement in eGFR suggests possible reversibility of renal dysfunction with immunosuppression. However, no change in alkali requirement indicates permanent damage as may be suggested by complete absence of H+–ATPase in the collecting ducts of two patients of pSS with RTA [22, 23]. One of the patients had pyuria at the time of renal biopsy, but the other had normal urine evaluation. The only method to assess response to therapy in such patients is repeat biopsy which could not be done in our patient. We suggest that patients with tubular dysfunction should undergo a renal biopsy to guide immunosuppressive therapy and to assess response to treatment.

The baseline ESSDAI was higher in the renal group primarily because of the higher weightage given to renal domain. There was a notable improvement in the ESSDAI at follow-up in the renal group suggesting that it may serve as a sensitive indicator of assessment of response to therapy. A previous study had observed that patients with pSS had a high neutrophil/lymphocyte ratio (NLR) which had a positive correlation with Sjogren's Syndrome Disease Activity Index (SSDAI) [37]. However, no change was observed in NLR during the study period.

Patients with and without RTA were also compared. The mean age, the age at onset and the age at diagnosis was almost 7 years lesser in RTA group, an observation similar to other Asian and Western series [7, 38]. These patients had less ocular sicca and articular manifestations. RTA was an early manifestation and commonly occurred before the onset of sicca symptoms similar to earlier observations [14, 16, 19, 20].

The characteristic histopathological feature of TIN is predominant CD4+ lymphocytic infiltration of the renal interstitium surrounding the renal tubules [16] similar to that seen in salivary glands [11]. The glandular epithelium is constantly stimulated by toll-like receptors (TLR) 3 and TLR 7 agonists leading to activation of epithelial and dendritic cells [39] and increased HLA-DR expression [40] which has also been observed in renal tubular epithelial cells during kidney disease [41, 42]. Thus, the glandular and renal interstitial infiltration may share the same pathogenesis, and certainly, epithelial cells are the first target in the pathogenesis of pSS as suggested by early infiltration of epithelia by inflammatory cells [39]. This may explain the early occurrence of RTA in pSS.

Moreover, NCCT and CA antigens are present both in salivary glands and renal intercalated cells [43]. Injury to salivary glands may stimulate an immune response against them. Antibodies against these antigens may have a role in the pathogenesis of RTA in pSS [27, 44]. Studies from neonatal lupus have shown that anti-SSA/SSB antibodies can be present asymptomatically for a long duration [45, 46]. Similarly, the antibodies against NCCT and CA may be present in serum asymptomatically for a long time and may be responsible for early-onset RTA.

The study had a few limitations. The sample size was small, which may be inadequate to detect few of the differences in the two groups. Being a single-center study, subjects belonged to a single ethnicity. Hence, the results need validation in different races and ethnicities. Ours is a tertiary care center. Patients with suspected Sjogren's syndrome including patients diagnosed with dRTA are referred to our department for evaluation. Hence, a referral bias is inherent to the study design. Renal biopsy was not done at follow-up in patients to assess the response to therapy. Measurement of antibodies against NCCT and CA antigens was also not performed. The duration of follow-up was short compared to the long natural history of the disease hampering the assessment of the long-term impact of renal involvement in pSS.

Thus, pSS patients with dRTA appear to be a distinct subgroup presenting at an early age with renal manifestations, less of sicca and articular manifestations but more of cutaneous vasculitis and a higher anti-SSA/SSB antibody positivity. All patients with pSS should undergo UAT to detect renal tubular defects, and those with iRTA should be followed up lest they develop complete RTA. All patients with RTA should undergo a renal biopsy to guide further immunosuppressive therapy which needs to be evaluated further in long-term studies.

**Acknowledgements** The authors thank Dr. Gunjan Kumar, Senior resident PSM, for statistical analysis.

**Author contributions** (1) The conception and design of the study—AJ, SBH, SP, and VSN. Acquisition of data—AJ, SBH, DE, and VKJ. Analysis and interpretation of data—AJ, SBH, DE, and VKJ. (2) Drafting the article—AJ, DE, and VKJ. Revising it critically for important intellectual content—SBH, SP, and VSN. (3) Final approval of the version to be submitted—AJ, SBH, DE, VKJ, SP, and VSN. (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved—AJ, SBH, DE, VKJ, SP, and VSN.

**Funding** This study was funded by Intramural Research fund, Jawaharlal Institute of Postgraduate Medicine and Research (Grant number: JIP/Res/Intra-DM, M.Ch/01/2015-16 and JIP/Res/Intra-DM, M.Ch/phas1/grant2/01/2016-17).

## Compliance with ethical standards

**Conflict of interest** None of the authors have any conflict of interest to declare.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approved by the Institute Ethics Committee of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, held on 11th December, 2014 (JIP/IEC/2014/8/441).

**Informed consent** Informed consent was obtained from all individual participants included in the study.

## References

1. Malladi AS (2012) Primary Sjogren's syndrome as a systemic disease: a study of participants enrolled in an international Sjogren's syndrome registry. Arthritis Care Res 64:911–918
2. Cimaz R (2003) Primary Sjogren syndrome in the paediatric age: a multicentre survey. Eur J Pediatr 162:661–665
3. Lin DF (2010) Clinical and prognostic characteristics of 573 cases of primary Sjogren's syndrome. Chin Med J (Engl) 123:3252–3257
4. Sandhya P, Jeyaseelan L, Scofield RH, Danda D (2015) Clinical characteristics and outcome of primary Sjogren's syndrome: a large asian indian cohort. Open Rheumatol J 9:36–45. https://doi.org/10.2174/1874312901409010036
5. Francois H, Mariette X (2016) Renal involvement in primary Sjogren syndrome. Nat Rev Nephrol 12(2):82–93. https://doi.org/10.1038/nrneph.2015.174
6. Both T, Hoorn EJ, Zietse R, van Laar JA, Dalm VA, Brkic Z, Versnel MA, van Hagen PM, van Daele PL (2015) Prevalence of distal renal tubular acidosis in primary Sjogren's syndrome. Rheumatology 54(5):933–939. https://doi.org/10.1093/rheumatology/keu401
7. Ren H (2008) Renal involvement and follow-up of 130 patients with primary Sjogren's syndrome. J Rheumatol 35:278–284
8. Pertovaara M, Korpela M, Kouri T, Pasternack A (1999) The occurrence of renal involvement in primary Sjogren's syndrome: a study of 78 patients. Rheumatology 38(11):1113–1120
9. Maripuri S, Grande JP, Osborn TG, Fervenza FC, Matteson EL, Donadio JV, Hogan MC (2009) Renal involvement in primary Sjogren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol 4(9):1423–1431. https://doi.org/10.2215/CJN.00980209
10. Jasiek M, Karras A, Le Guern V, Krastinova E, Mesbah R, Faguer S, Jourde-Chiche N, Fauchais A-L, Chiche L, Dernis E, Moulis G, Fraison J-B, Lazaro E, Jullien P, Hachulla E, Le Quellec A, Rémy P, Hummel A, Costedoat-Chalumeau N, Ronco P, Vanhille P, Meas-Yedid V, Cordonnier C, Ferlicot S, Daniel L, Seror R, Mariette X, Thervet E, François H, Terrier B (2017) A multicentre study of 95 biopsy-proven cases of renal disease in primary Sjögren's syndrome. Rheumatology 56(3):362–370. https://doi.org/10.1093/rheumatology/kew376
11. Evans RD, Laing CM, Ciurtin C, Walsh SB (2016) Tubulointerstitial nephritis in primary Sjogren syndrome: clinical manifestations and response to treatment. BMC Musculoskeletal Disord 17:2. https://doi.org/10.1186/s12891-015-0858-x
12. Vitali C (2002) Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61:554–558
13. Walsh SB, Shirley DG, Wrong OM, Unwin RJ (2007) Urinary acidification assessed by simultaneous furosemide and fludrocortisone treatment: an alternative to ammonium chloride. Kidney Int 71(12):1310–1316. https://doi.org/10.1038/sj.ki.5002220
14. Goules A (2000) Clinically significant and biopsy-documented renal involvement in primary Sjogren syndrome. Medicine 79:241–249
15. Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG (2013) Clinically significant renal involvement in primary Sjogren's syndrome: clinical presentation and outcome. Arthritis Rheumat 65(11):2945–2953. https://doi.org/10.1002/art.38100
16. Bossini N, Savoldi S, Franceschini F, Mombelloni S, Baronio M, Cavazzana I, Viola BF, Valzorio B, Mazzucchelli C, Cattaneo R, Scolari F, Maiorca R (2001) Clinical and morphological features of kidney involvement in primary Sjogren's syndrome. Nephrol Dialysis Transpl 16(12):2328–2336
17. Ramos-Casals M (2014) Systemic involvement in primary Sjogren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology 53:321–331
18. Ramos-Casals M (2008) Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine 87:210–219
19. Sandhya P, Danda D, Rajaratnam S, Thomas N (2014) Sjogren's, renal tubular acidosis and osteomalacia—an Asian Indian series. Open Rheumatol J 8:103–109. https://doi.org/10.2174/1874312901408010103
20. Ram R, Swarnalatha G, Dakshinamurty KV (2014) Renal tubular acidosis in Sjogren's syndrome: a case series. Am J Nephrol 40(2):123–130. https://doi.org/10.1159/000365199
21. Goroshi M, Khare S, Jamale T, Shah NS (2016) Primary Sjogren's syndrome presenting as hypokalemic paralysis: a case series. J Postgrad Med. https://doi.org/10.4103/0022-3859.194224
22. Cohen EP (1992) Absence of H+-ATPase in cortical collecting tubules of a patient with Sjogren's syndrome and distal renal tubular acidosis. J Am Soc Nephrol 3:264–271
23. DeFranco PE, Haragsim L, Schmitz PG, Bastani B (1995) Absence of vacuolar H+-ATPase pump in the collecting duct of a patient with hypokalemic distal renal tubular acidosis and Sjogren's syndrome. J Am Soc Nephrol 6:295–301
24. Pertovaara M, Bootorabi F, Kuuslahti M, Pasternack A, Parkkila S (2011) Novel carbonic anhydrase autoantibodies and renal manifestations in patients with primary Sjogren's syndrome. Rheumatology 50:1453–1457
25. Takemoto F (2007) Induction of anti-carbonic-anhydrase-II antibody causes renal tubular acidosis in a mouse model of Sjogren's syndrome. Nephron Physiol 106:63–68
26. van den Wildenberg MJ, Hoorn EJ, Mohebbi N, Wagner CA, Woittiez AJ, de Vries PAM, Laverman GD (2015) Distal renal tubular acidosis with multiorgan autoimmunity: a case report. Am J Kidney Dis 65(4):607–610. https://doi.org/10.1053/j.ajkd.2014.09.026
27. Kim YK (2008) Acquired Gitelman syndrome in a patient with primary Sjogren syndrome. Am J Kidney Dis 52:1163–1167
28. Aasarod K, Haga HJ, Berg KJ, Hammerstrom J, Jorstad S (2000) Renal involvement in primary Sjogren's syndrome. QJM 93:297–304

29. Talal N, Zisman E, Schur PH (1968) Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjogren's syndrome. Arthritis Rheum 11:774–786
30. Vitali C, Tavoni A, Sciuto M, Maccheroni M, Moriconi L, Bombardieri S (1991) Renal involvement in primary Sjogren's syndrome: a retrospective-prospective study. Scand J Rheumatol 20(2):132–136
31. Siamopoulos KC, Elisaf M, Drosos AA, Mavridis AA, Moutsopoulos HM (1992) Renal tubular acidosis in primary Sjogren's syndrome. Clin Rheumatol 11(2):226–230
32. Eriksson P, Denneberg T, Granerus G, Lindstrom F (1996) Glomerular filtration rate in primary Sjogren's syndrome with renal disease. Scand J Urol Nephrol 30(2):121–127
33. Preminger GM, Sakhaee K, Pak CY (1987) Hypercalciuria and altered intestinal calcium absorption occurring independently of vitamin D in incomplete distal renal tubular acidosis. Metabol Clin Exp 36(2):176–179
34. Preminger GM, Sakhaee K, Skurla C, Pak CY (1985) Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. J Urol 134(1):20–23
35. Kim HY, Kim SS, Bae EH, Ma SK, Kim SW (2015) Decreased renal expression of H(+)-ATPase and pendrin in a patient with distal renal tubular acidosis associated with Sjogren's syndrome. Internal Med 54(22):2899–2904. https://doi.org/10.2169/internalmedicine.54.4821
36. Ramos-Casals M, Brito-Zeron P, Seror R, Bootsma H, Bowman SJ, Dorner T, Gottenberg JE, Mariette X, Theander E, Bombardieri S, De Vita S, Mandl T, Ng WF, Kruize A, Tzioufas A, Vitali C, Force ESST (2015) Characterization of systemic disease in primary Sjogren's syndrome: EULAR-SS Task Force recommendations for articular, cutaneous, pulmonary and renal involvements. Rheumatology 54(12):2230–2238. https://doi.org/10.1093/rheumatology/kev200
37. Hu ZD, Sun Y, Guo J, Huang YL, Qin BD, Gao Q, Qin Q, Deng AM, Zhong RQ (2014) Red blood cell distribution width and neutrophil/lymphocyte ratio are positively correlated with disease activity in primary Sjogren's syndrome. Clin Biochem 47(18):287–290. https://doi.org/10.1016/j.clinbiochem.2014.08.022
38. Shiozawa S, Shiozawa K, Shimizu S, Nakada M, Isobe T, Fujita T (1987) Clinical studies of renal disease in Sjogren's syndrome. Ann Rheum Dis 46(10):768–772
39. Nocturne G, Mariette X (2013) Advances in understanding the pathogenesis of primary Sjogren's syndrome. Nat Rev Rheumatol 9(9):544–556. https://doi.org/10.1038/nrrheum.2013.110
40. Tsunawaki S (2002) Possible function of salivary gland epithelial cells as nonprofessional antigen-presenting cells in the development of Sjogren's syndrome. J Rheumatol 29:1884–1896
41. Fukatsu A (1993) Expression of interleukin 6 and major histocompatibility complex molecules in tubular epithelial cells of diseased human kidneys. Lab Invest 69:58–67
42. Oren R (1995) C3, C4, factor B and HLA-DR [alpha] mRNA expression in renal biopsy specimens from patients with IgA nephropathy. Immunology 86:575–583
43. Kim J, Tisher CC, Linser PJ, Madsen KM (1990) Ultrastructural localization of carbonic anhydrase II in subpopulations of intercalated cells of the rat kidney. J Am Soc Nephrol 1:245–256
44. Inagaki Y, Jinno-Yoshida Y, Hamasaki Y, Ueki H (1991) A novel autoantibody reactive with carbonic anhydrase in sera from patients with systemic lupus erythematosus and Sjogren's syndrome. J Dermatol Sci 2:147–154
45. McCune AB, Weston WL, Lee LA (1987) Maternal and fetal outcome in neonatal lupus erythematosus. Ann Intern Med 106(4):518–523
46. Press J, Uziel Y, Laxer RM, Luy L, Hamilton RM, Silverman ED (1996) Long-term outcome of mothers of children with complete congenital heart block. Am J Med 100(3):328–332. https://doi.org/10.1016/s0002-9343(97)89492-2