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Renal Tubular Acidosis in Primary Sjögren's Syndrome

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Summary **Renal tubular acidosis (RTA) is a frequent extraglandular manifestation of Sjögren's syndrome; however, no distinction on the incidence of this renal tubular defect between primary and secondary Sjögren's syndrome has been reported. This study was undertaken in order to define the frequency of RTA and the possible pathogenetic mechanisms in a group of 21 randomly selected primary Sjögren's syndrome patients. RTA was found in 7 (33%) patients. The incomplete type of the disorder was the most frequent. It seems that the etiology of RTA is multifactorial. Renal excretion of monoclonal proteins and the immunologically-induced interstitial inflammation are the main possible factors of this renal tubular defect.**

Key words: **Sjögren's Syndrome, Renal Tubular Acidosis (RTA), Nephrolithiasis, Interstitial Nephritis, Serum Monoclonal Proteins, Urine Monoclonal Proteins.**

INTRODUCTION

Sjögren's syndrome (SS) an autoimmune exocrinopathy can occur as an entity alone (primary SS) or in association with any other autoimmune rheumatic disorder, most frequently with rheumatoid arthritis, systemic lupus erythematosus and scleroderma (secondary SS) (1). Patients with primary SS (pSS) express a diverse clinical spectrum expanding from organ specific to systemic autoimmune disease. In some patients the disorder evolves to B-cell neoplasia (2).

Clinical and more often subclinical kidney involvement is a well documented extraglandular manifestation of SS. The most common histopathological lesion reported is an interstitial lymphocyte infiltration with tubular atrophy and fibrosis (3). The clinical presentation of this lesion may be overt or latent distal renal tubular acidosis (4,5), the Fanconi's syndrome and other defects of renal tubular function (3,4,6-8). In most studies, however, the patients' selection criteria were not well defined and some of the patients studied could be characterized as suffering from secondary SS.

We untertook the current study to define the prevalence of renal tubular acidosis (RTA) in a group of patients with pSS and to correlate this functional abnormality with clinical and laboratory parameters.

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MATERIALS AND METHODS

Patients

Twenty-one randomly selected female pSS patients with a mean age of 50 (35-66) years and mean duration of pSS symptoms 6.5 (1-18) years were studied. All patients satisfied at least two of the three following criteria for the diagnosis of SS: keratoconjunctivitis sicca (positive Rose-Bengal staining), xerostomia (decreased parotid flow rate less than 0.5ml/5min/gland) and recurrent parotid gland enlargement. The diagnosis was confirmed in all patients with a labial minor salivary gland biopsy which showed focal lymphocyte infiltrates greater than 2+ (9). None of these patients had clinical or serological abnormalities characteristic of any other autoimmune disease and none of them were receiving drugs known to interfere with renal tubular function. Informed consent was obtained by all patients participating in the study.

Methods

Biographical data of the patients including: sex, age of disease onset, disease duration and sings or symptoms of extraglandular manifestations such as Raynaud's phenomenon (R), arthralgias (A), purpura (P), peripheral neuropathy (PN), splenomegely (S), gastrointestinal and liver involvement, lung involvement and lymphadenopathy were taken from the patients records. In

Table I: *Clinical and laboratory characteristics of the patients*

Patient N°	Age (yrs)	Mean duration of the disease (yrs)	Extraglandular manifestations R	A	L	GI	CAH	Lymphadenopathy	Creatinine clearance (ml/min)	RTA
1	60	8	−	+	−	+	(−)	(−)	84	complete
2	40	18	−	−	+	−	(−)	(−)	80	complete
3	66	4	−	−	−	−	(+)	(+)	85	incomplete
4	72	1	−	−	+	+	(−)	(+)	78	incomplete
5	46	1	+	+	−	−	(−)	(−)	90	incomplete
6	46	10	+	−	−	ND	(−)	(−)	68	incomplete
7	57	12	+	−	−	−	(−)	(−)	96	incomplete
8	66	1	+	+	−	−	(−)	(−)	76	NO
9	39	1	−	+	+	−	(−)	(−)	80	NO
10	53	13	+	−	−	−	(−)	(−)	82	NO
11	57	4	−	+	−	−	(−)	(−)	79	NO
12	35	10	−	+	−	−	(−)	(−)	88	NO
13	71	2	+	−	+	+	(−)	(+)	90	NO
14	49	12	+	+	+	+	(−)	(−)	92	NO
15	59	8	+	+	−	+	(−)	(−)	84	NO
16	50	1	−	+	+	−	(−)	(+)	102	NO
17	46	5	+	−	−	+	(−)	(−)	88	NO
18	37	4	+	+	−	−	(+)	(−)	90	NO
19	48	1	+	+	−	−	(−)	(+)	50	NO
20	63	1	−	−	−	+	(−)	(+)	84	NO
21	61	1	−	−	−	−	(−)	(−)	86	NO

R = Raynaud's phenomenon, A = arthralgias, L = lung disease, GI = gastrointestinal involvement, CAH = chronic active hepatitis, RTA = renal tubular acidosis, ND = not done.

addition, the latest laboratory data including: antinuclear antibodies (ANA), antibodies to Ro (SSA) and La (SSB) antigens, rheumatoid factor (RF) and serum complement components C_3-C_4 were also taken. All patients were studied on an outpatient basis. They were asked to collect a 24/hour urine sample which was sent to the laboratory for measurement of total protein excretion, calcium, and creatinine as well as for the demonstration and identification of monoclonal proteins by a high resolution agarose gel electrophoresis technique (HRAGE) combined with immunofixation (10-13). At the time of arrival (8.00 a.m.), the patients were advised to give a urine specimen for microscopic examination, pH measurement and culture. Arterial blood was also taken for measurements of pH and HCO_3^-, while venous blood for measurements of creatinine, electrolytes, total protein and globulins, as well as for the demonstration and characterization of cryoglobulins (12,13) was obtained. Serum monoclonal proteins were also tested with HRAGE. Urinary concentrating ability was studied using the protocol of Gyory et al (14).

In order to reveal the frequency of the incomplete type of RTA, an acute acid loading test using the method of Wrong and Davis (15) was performed in the nonacidotic patients. Finally, patients without available recent kidney X-rays were submitted to renal ultrasonographic studies for detection of calcifications and or renal stones. Statistical analysis was performed using the student's t-test and chi-square test.

RESULTS

The clinical and laboratory characteristics of the patients are shown in Table I. RTA was diagnosed in 7 patients (2 with the complete and 5 with the incomplete type). Urinary concentrating ability was diminished in the 2 patients with the complete type of RTA. Extraglandular manifestations were present in the majority of the patients. Six patients had lung involvement (L) such as xerotrachea (16) and restrictive lung disease (DLCO < 70% predicted). Seven of the 20 patients tested had gastrointestinal involvement (GI) mainly oesophageal dysfunction (17). None of the patients had hypergammaglobulinemic purpura, peripheral neuropathy or splenomegaly either before or during the study.

In two patients (No. 2 and 6) nephrolithiasis was found. Both of them had also hypercalciuria (24 h urine calcium 380 and 360 respectively). In the remaining patients urine calcium was within normal limits (< 250 mg/24h). Severe proteinuria (24 hour urine protein > 3.5g) was found in patients No. 9 and 19. Both patients underwent

Table II: *Immunological profile of the patients*

Patients No	ANA titer	C3/C4 mg/dl	RF titer	Serum a-Ro (SSA)	Serum a-La (SSB)	Cryoglobulins	Serum HRAGE	Urine HRAGE
1	1/80	33/51	1/40	–	–	–	–	–
2	1/2560	60/20	1/80	+	+	–	–	–
3	1/5120	110/34	1/20	–	–	+	IgGk	k
4	1/80	134/49	–	–	–	–	–	–
5	1/80	245/72	1/80	+	–	–	–	–
6	1/320	71/3	1/320	+	+	+	IgMk	I gMk,k
7	1/80	82/62	1/160	–	–	–	IgMk	k
8	1/80	82/29	–	–	–	–	–	–
9	1/80	94/37	–	–	–	–	–	IgGλ
10	1/80	111/37	–	+	–	–	–	–
11	1/80	98/40	1/160	+	–	–	–	–
12	1/1280	86/32	1/80	+	–	–	–	–
13	1/2560	120/26	1/1280	+	+	+	–	–
14	1/2560	107/28	1/80	+	+	+	–	–
15	1/1280	148/44	–	ND	ND	–	–	–
16	1/1280	111/33	1/320	+	–	–	–	–
17	1/80	98/27	–	–	–	–	–	–
18	1/1280	107/39	1/160	–	–	–	–	–
19	1/1280	90/33	1/40	+	+	+	–	–
20	1/80	63/20	–	–	–	–	–	–
21	1/80	84/42	1/80	+	+	–	–	–

+ = positive, – = negative, ND = not done.

a kidney biopsy. Membranoproliferative and membranous glomerulonephritis were diagnosed respectively. Apart from patient No 19 and with respect to age, creatinine clearances were within normal range. Serum potassium was at the lower or below the normal values in the first two patients.

The immunological profile of our patients is shown in Table II. In 10 patients ANA titers were above normal values (>1/80). In 2 out of the 21 patients (No 1 and 6) C_3 or C_4 serum levels were below the normal values. RF was above the normal values (>1/40) in 11 patients. Antibodies to Ro (SSA) antigen were found in 11 out of the 20 patients tested, while anti−La (SSB) antibodies were identified in 6 out of the 20 patients. Mixed monoclonal cryoglobulins (IgMk) were demonstrated in the sera of 5 patients (2 with and 3 without RTA). Three patients all of whom had RTA had monoclonal immunoglobulins in their sera. Urine immunoglobulins either IgGλ or IgMk as well as free light chains k were detected in 4 patients (3 with and 1 without RTA).

Table III shows the comparison between patients with and those without renal tubular acidification defect. The mean age and the duration of the disease were not significantly different in the two groups. Regarding the incidence of extraglandular manifestations, we found that arthralgias were less frequent in patients with RTA ($p<0.05$). Creatinine clearance, hypergammaglobulinemia, and the incidence of antibodies to Ro (SSA) and La (SSB) were not significantly different in the two groups. Also no difference between the two groups was observed in the percentage of patients with serum cryoglobulins, positive ANA and RF. Patients with RTA had increased incidence of low C3/C4 ($p<0.05$) as well as serum and urine monoclonal proteins ($p<0.05$, $p<0.05$ respectively).

No correlation between the severity of lymphocyte infiltration of minor labial salivary gland and the development of RTA was found.

DISCUSSION

Complete or incomplete RTA is a frequent extraglandular manifestation of SS. According to previous studies this renal tubular defect may be present in 22 to 30% of SS patients (5,6). These studies, however, have been published almost 10 years before the distinction was made between primary and secondary SS by Moutsopoulos et al (1). Thus, it could be argued that some of the patients studied probably had secondary SS. In our

Table III: *Comparison of patients with or without renal tubular acidosis (RTA)*

	with RTA	without RTA	Statistical significance
Patients (No)	7	14	
Age (mean ± SD) years	55.0 ± 11.7	52.0 ± 11.0	NS
Mean duration of disease (mean ± SD) years	7.7 ± 6.2	4.5 ± 4.4	NS
Extraglandular manifestations			
Raynaud's phenomenon	3/7 (43%)	8/14 (57%)	NS
Arthralgias	2/7 (29%)	9/14 (64%)	$p<0.05$
Lung involvement	2/7 (29%)	4/14 (29%)	NS
GI involvement	2/6 (33%)	5/14 (36%)	NS
Liver involvement	1/7 (14%)	1/14 (7%)	NS
Lymphodenopathy	2/7 (29%)	4/14 (29%)	NS
Creatinine clearance (ml/min)	83 ± 8.9	83.6 ± 11.6	NS
Patients with			
Ro-SSA (%)	3/7 (43%)	8/13 (62%)	NS
La-SSB (%)	2/7 (29%)	4/13 (30%)	NS
Serum cryoglobulins (%)	2/7 (29%)	3/14 (21%)	NS
Low C3/C4 (%)	2/7 (29%)	0/14 (0%)	$p<0.05$
RF > 1 : 40 (%)	4/7 (57%)	7/14 (50%)	NS
ANA > 1 : 80 (%)	3/6 (50%)	7/13 (54%)	NS
Hypergammaglobulinemia (>20g/L)	3/7 (43%)	7/14 (50%)	NS
Serum monoclonal proteins (%)	3/7 (43%)	0/14 (0%)	$p<0.05$
Urine monoclonal proteins (%)	3/7 (43%)	1/14 (7%)	$p<0.05$

study, we found that 33% of unselected patients with pSS had either complete or incomplete RTA. Since renal function was within normal limits and no other disorders associated with RTA were evident in our patients, we suggest that RTA is a frequent extraglandular manifestation of pSS which is attributed to the disease.

The pathophysiology of RTA has been debated in the literature (18,19). Although the most common histological renal lesion is interstitial nephritis, it is unclear whether the reported renal tubular defects are the direct result of the interstitial inflammatory process. Various studies (5,18,20,21) have suggested that lymphocyte and plasma cell infiltrates surrounding renal tubules are associated with and may cause a renal tubular defect. Like Shioji et al (18), however, we also noted that RTA was not always associated with the demonstration of interstitial infiltrate in renal biopsies (22). Thus, it seems unlikely that interstitial nephritis is the sole cause for the development of RTA in pSS. It could be assumed that the reported high rate of correlation between RTA and interstitial renal lesion in previous studies is due to the fact that some of the patients studied were secondary SS patients. Although it is well known that both rheumatoid arthritis and systemic lupus erythematosus (SLE) are associated with interstitial renal lesion (23–25), no correlation was found between the histological findings and renal tubular functional disturbances in patients with SLE (24,25). It has been reported that SS patients with RTA were younger and had longer disease duration than those without RTA (7). In contrast to this study we found no statistically significant differences between patients with and without RTA regarding the age and the duration of the disease. The findings of Shiozawa et al (7) are probably due to the lower creatinine clearance, which was also observed in their patients with RTA.

Renal involvement is associated with other systemic extraglandular manifestations (4) of SS. Since we observed no differences on the incidence of Raynaud's phenomenon, lung and gastrointestinal involvement between patients with and without RTA, we suggest that the reported association is related to the glomerulonephritis of SS rather than to the renal tubular defects. The observation of the increased incidence of arthralgias in patients without RTA is probably due to the subjectivity of this symptom.

No difference was observed between the two groups with respect to the incidence of various autoantibodies and serum cryoglobulins. Although cryoglobulinemia is associated with the glomerulonephritis of SS, it seems that cryoglobulins like hypergammaglobulinemia are not the major causes for the development of RTA in pSS (4,18,26).

The demonstration and identification of monoclonal proteins in the blood and the urine of patients with pSS was previously reported (11). The possibility of a "toxic" effect of these monoclonal proteins on the renal tubules was investigated and our results support this assumption. Whereas, monoclonal proteins were not detected

in all RTA patients tested, it was detected in one patient without RTA.

Finally, we found two RTA patients with low C_3 or C_4. Low serum C_3 levels were reported in pSS patients with glomerulonephritis (27); C_3 and immunoglobulins were also identified in the renal tubules (20,21). Whether the deposition of complement to the renal tubules causes the low serum levels of C_3 and C_4 and whether this finding suggests the immunologically-mediated renal tubular impairment in our patients, is only an assumption at present. Thus, based on our findings we suggest that RTA is a frequent extraglandular manifestation of pSS but the pathogenesis is still unresolved. Among the various mechanisms involved, renal excretion of monoclonal proteins and the immunologically-mediated inflammation seem to be the most important causative factors in the multifactorial nature of this renal tubular abnormality.

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