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Subclinical renal tubular acidosis in patients with primary and secondary Sjögren's syndrome: a possible marker of disease progression

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Abstract To clarify the prevalence of subclinical renal tubular acidosis (RTA) and its association with clinical and laboratory parameters in primary and secondary Sjögren's syndrome (SS), an acid-loading test was conducted. Subclinical RTA was found in 32% of patients with SS. The prevalence of subclinical RTA in primary and secondary SS was about the same (31.6% and 33.3%, respectively). Significant longer duration of illness, more severely decreased salivary excretion, decreased lymphocyte number, higher serum levels of IgG and IgA, and higher frequency of anti-SS-A (Ro) and SS-B (La) antibodies were found in patients with subclinical RTA. These results suggested that subclinical RTA may be a characteristic manifestation both in primary and secondary SS, along with the progression of immunologic dysfunction, when the illness seemed to be indolent.

Key words Extraglandular involvement · Renal tubular acidosis (RTA) · Sjögren's syndrome (SS)

Introduction

Sjögren's syndrome (SS) is a chronic inflammatory disease characterized by the infiltration of lymphocytes into the lacrimal and salivary glands, which results in dry eyes and dry mouth. The syndrome sometimes involves extraglandular organs affecting the kidneys, lungs, blood vessels, and other organs.[1] Lymphocytes infiltrating tubular lesions of the kidney are considered responsible for various functional abnormalities, such as renal tubular acidosis (RTA), nephrogenic diabetes insipidus, or Fanconi's syndrome.[2] Of these functional abnormalities, RTA is sometimes associated with nephrocalcinosis,[3–6] whereas overt RTA in SS is actually less common. Overt renal disease has been reported to appear in 4.2% of patients with primary SS by a 15-year follow-up study.[7] On the other hand, approximately 15%–50% of primary SS patients manifest abnormal urine acidification at subclinical levels.[8–10] The clinical significance of subclinical (latent) RTA in primary SS has not been established. Even less is understood about the prevalence of subclinical RTA in secondary SS complicated by other rheumatic diseases.

The present study examines the ability to acidify urine in distal tubules in response to an acid load in patients with either primary or secondary SS. The results were analyzed in relation to clinical and laboratory parameters.

The results suggested that subclinical RTA (type I) is a characteristic event of the clinical course in both primary and secondary SS, and may reflect progression of the disease.

Patients and methods

Patients

Fifty-three patients with SS were enrolled in this study. All patients fulfilled the criteria for diagnosis of SS by the Japanese Research Group for Autoimmune Disease.[11] These enrolled patients also fulfilled the diagnostic criteria for the classification of SS by the European Community,[12] and for the classification of definite SS by Fox et al.[13] The patients in this study consisted of 50 female and 3 male patients, and the mean age was 55.3 years (22–88 years). Primary SS was diagnosed in 38 patients and secondary SS in 15 patients. Among the latter, five had rheumatoid arthritis (RA), five had systemic lupus erythematosus (SLE), three had mixed connective tissue disease (MCTD), and two had systemic sclerosis (SS). None of the patients had abnormal values of serum electrolytes, urea nitrogen,

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serum creatinine, blood pH, or complications of multiple myeloma, hyperthyroidism, urinary tract infection, or arterial hypertension, which are causative factors of RTA. Five patients with RA, five patients with SLE, and one patient with MCTD, all of whom were without SS, were enrolled as control patients. Nine female volunteers (ages 26–58 years; mean 44.4 years) were also enrolled in this study as normal controls.

Acid-loading test

An acid-loading test, which detects type I RTA by distal tubular dysfunction, was performed as described by Wrong and Davies.[14] In brief, ammonium chloride powder in gelatin capsules was ingested (0.1 g/kg) within 1 h. Urine was collected beforehand and at hourly intervals for 6 h thereafter. Urinary pH was immediately measured using a glass electrode pH meter. From the results of normal controls and the literature,[14] a decrease of urinary pH to less than 5.3 at any time was regarded as normal acid excretion. None of the normal volunteers showed abnormal results with the acid-loading test. Written informed consent for the acid-loading test was obtained from all patients before starting the study. Blood gas analysis, liver function tests, and blood ammonium levels were examined before the test, and patients with any prior abnormal results were excluded from this study.

Clinical and laboratory parameters

The results of the acid-loading test were compared with the age of patients, duration of illness (months after the first oral or keratoconjunctive sicca symptoms or the first parotid gland swelling were recognized), and salivary output at the time of the test. The results were also compared with laboratory parameters including hemoglobin concentration, numbers of leukocytes and platelets, serum immunoglobulin and gammaglobulin levels, titer and frequency of anti-nuclear antibody, frequency of positive anti-Ro (SS-A) and anti-La (SS-B) antibodies, serum nitrogen and creatinine levels, excretion of urinary beta-2-microglobulin (β_2-m), urinary N-acetyl-glucosamidase (NAG), and serum and urinary amylase levels at the time of acid loading. We also examined the association between the results of the acid-loading tests and the focus score in biopsy specimens of minor salivary glands. Biopsy specimens were obtained at the time of the diagnosis of SS in most patients, which preceded the acid-loading test by 7 to 146 months. One focus score was determined when the number of inflammatory cell aggregates, consisting of at least 50 cells, was present in each 4 mm^2 of salivary gland tissue.[15]

Stimulated whole salivary secretion

The production of stimulated whole salivary secretion was quantified. In brief, patients were asked to chew gum for 10 min 2 h after each meal. Total saliva flow was measured each time, and a mean saliva flow less than 9.9 ml/10 min was considered to be abnormaly decreased. In normal age-matched individuals, mean saliva flow was 14.4 ± 2.6 ml/10 min.

Statistical analysis

Results were statistically analyzed using the Mann-Whitney test and by determining Pearson's correlation coefficient. P-value <0.05 was considered significant.

Results

Subclinical RTA in primary and secondary SS

Subclinical RTA was determined by acid loading in 32% of patients with SS. The prevalence of subclinical RTA between primary and secondary SS did not differ (31.6% and 33.3%, respectively) (Table 1). In secondary SS, subclinical RTA was distributed in any underlying rheumatic diseases. None of the RA, SLE, or MCTD patients without SS presented with abnormal urine acidification results (data not shown).

Correlation of subclinical RTA, and clinical and laboratory parameters

The results of acid-loading tests were compared with clinical and laboratory parameters (Table 2). A significantly longer duration of illness (90.5 vs 53.3 months) and more severe decrease of salivary excretion (3.85 vs 6.67 ml/10 min) was identified in patients with subclinical RTA.

The focus score at the time of the diagnosis of SS did not relate to the prevalence of subclinical RTA.

The number of peripheral blood lymphocytes was decreased severely in patients with subclinical RTA (1043 vs 1859 cells/μl), although the total number of peripheral white blood cells in both groups did not differ.

Serum levels of IgA and IgG, but not IgM, were higher in patients with subclinical RTA than in those without subclinical RTA (2044 vs 1717 mg/dl, IgG; 462 versus 312 mg/dl, IgA), although the serum levels of total gammaglobulin were the same in both groups.

The frequency and titer of anti-nuclear antibody and rheumatoid factor did not differ in either group. On the

Table 1. Subclinical RTA in primary and secondary SS

	Number of patients	Subclinical RTA present
Primary SS	38	12 (31.6%)
Secondary SS	15	5 (33.3%)
Total	53	17 (32.0%)

RTA, renal tubular acidosis; SS, Sjögren's syndrome

Table 2. Correlation of subclinical RTA, and clinical and laboratory parameters

	Subclinical RTA		*P* value (present versus absent)
	Present ($n = 17$)	Absent ($n = 36$)	
Age (mean; years)	53.9	56.7	NS
Duration of illness (years)	7.65	4.53	0.03
Salivary excretion rate (ml/10 min)	3.85	6.67	0.02
Focus score	2.50	2.18	NS[a]
Hemoglobin concentration [11.3–15.2 g/dl]	11.8	11.8	NS
Number of platelets [13.0–36.4 $\times$ 10^4/μl]	15.2	16.6	NS
Number of peripheral leukocytes [3900–9800/μl]	4467	5200	NS
Number of peripheral lymphocytes [1500–3800/μl]	1043	1859	0.01
Serum gammaglobulin level [1.04–1.53 g/dl]	1.75	1.66	NS
Serum IgG level [780–1520 mg/dl]	2044	1717	0.04
Serum IgA level [94–418 mg/dl]	462	312	0.01
Serum IgM level [67–268 mg/dl]	172	155	NS
Serum amylase level [60–200 IU/l, 37°C]	851	305	NS
Urinary amylase level [160–960 IU/l, 37°C]	967	1055	NS
Frequency of anti-nuclear antibody (%) [less than 40 dils]	94.1	94.4	NS
Titer greater than 320 dils (%)	62.5	51.5	NS
Frequency of positive SS-A (%) [less than 10 U/ml]	93.8	65.5	0.03
Frequency of positive SS-B (%) [less than 10 U/ml]	43.5	17.1	0.04
Frequency of positive rheumatoid factor (%) [less than 40 dils]	41.1	41.6	NS
Blood nitrogen [6–20 mg/dl]	18.2	15.5	NS
Serum creatinine level [0.6–1.6 mg/dl]	0.89	0.70	NS
Urinary beta-2 microglobulin [less than 230 μg/l]	3799	134	0.02
Urinary N-acetyl-glucosamidase [less than 7.0 U/l]	6.7	4.1	NS

NS, not significant; [ ], the reference value or reference limits in our hospital
[a] Number of biopsied specimens available for counting focus score was 13 cases with subclinical RTA and 28 cases without subclinical RTA

other hand, SS-A and SS-B antibodies were found more frequently in the patients with subclinical RTA (93.8% versus 65.5%, SS-A; 43.5 versus 17.1%, SS-B antibodies).

Renal function tests showed that only β_2-m excretion into the urine was higher in the patients with subclinical RTA (3799 versus 134 μg/ml). Other laboratory indicators of renal function such as serum nitrogen and creatinine levels, urinary pH, frequency of proteinuria, and urinary NAG did not differ between the groups.

Subclinical RTA and other extraglandular organ involvement in primary and secondary SS

A mild interstitial pneumonia in one patient and cystic bronchiectasis in another patient were observed in primary SS with subclinical RTA. A pleural adhesion without pleural effusion in the lung base was observed in each five patients in primary or secondary SS, two of whom in each SS have subclinical RTA.

A lacrimal gland cyst was observed in a primary SS patient with subclinical RTA. Peripheral neuropathy, mainly a mononeuritis multiplex with sensory disturbance of upper and lower extremities, was observed in 11 patients with primary or secondary SS, with or without the diagnosis of subclinical RTA. Cryoglobulinemia with palpable purpura in the lower extremities was observed in two patients with primary SS, either with or without subclinical RTA. M proteinemia of IgM-kappa in secondary SS without RTA and IgA-kappa in primary SS with sub-clinical RTA were observed. Neoplastic diseases, including malignant lymphoma, were not found in any group of SS patients.

Discussion

SS is a systemic autoimmune disease that often involves glandular and extraglandular organs. Most renal involvement in SS occurs in tubular lesions,[8,16,17] which leads to different types of functional disorders. Although the glomerular damage in SS has been reported to be less frequent,[8,18–20] recent studies suggested that glomerular damages appear after a long duration of the illness.[7] Clinically, the prevalence of an overt renal tubular involvement is rare in SS.[21] Subclinical distal tubular acidosis (type I RTA), on the other hand, has been demonstrated by acid loading in approximately 15%–50% of patients with primary SS.[8–10,21,22] Little has been reported about the prevalence of subclinical RTA in secondary SS. Our results indicated that subclinical RTA occurs equally in both primary and secondary SS, in contrast to the report by Moutsopoulos et al.[23] The prevalence of subclinical RTA was not restricted to any specific rheumatic diseases among our patients with secondary SS.

Our results demonstrated that subclinical RTA is associated with the duration of illness. Shiozawa et al.[9] also reported that renal involvement is found in patients with a longer duration of primary SS. These observations suggest that subclinical RTA may be a characteristic manifestation both in primary and secondary SS, along with the progression of illness. Vitali et al.[22] identified two patients with primary SS and overt RTA among 104 with SS. Both of these patients had manifested a long duration of illness with other extraglandular manifestations. Whether or not subclinical RTA will progress to overt RTA remains obscure.

The association of the other extraglandular manifestations, such as pulmonary, neurologic, and hematologic involvement, and subclinical RTA, is not conclusive in our study. The clinical relevance of latent alveolitis in SS, confirmed by broncho-alveolar lavage in 44%–100% of patients with primary SS, has been detected after long-term prospective follow-up studies.[24,25]

With respect to the proximal tubular dysfunction, urinary β_2-m excretion is reported to be abnormal in 26% of primary SS patients with a higher prevalence than that of RTA (12%) in a group of patients.[26] Our results also demonstrated that mean β_2-m excretion in the urine was apparently higher in patients with subclinical RTA. Eleven of 17 patients with subclinical RTA showed abnormal excretion. On the other hand, 6 of 36 patients without subclinical RTA excreted abnormal amounts of β_2-m (data not shown). These results indicated that renal tubular dysfunction in both distal and proximal regions is not always overlapping.

The other important results of our study are that subclinical RTA is associated with several immunological markers such as polyclonal hypergammaglobulinemia, serum IgA and IgG levels, high frequency of autoantibodies such as SS-A/Ro and SS-B/La, and a decrease in the number of peripheral lymphocytes. The presence of anti-SS-A/Ro antibodies is associated with leukopenia.[27,28] Both anti-SS-A/Ro and anti-SS-B/La antibodies are also associated with extraglandular involvement.[29] Hypergammaglobulinemia and a higher frequency of autoantibodies are accompanied by extraglandular involvement.[30] Our results and others indicate that the incidence of extraglandular involvement, including subclinical renal tubular impairment, in SS are strongly associated not only with glandular damage but also with immunologic abnormalities.

In our study, the focus score did not correlate with the presence of subclinical RTA. All biopsy specimens were obtained at the time of initial diagnosis of SS but not at the time of acid-loading tests. This suggests that the immunological mechanisms responsible for the initial glandular dysfunction, and for the involvement of extraglandular organs over the course of the illness, may differ. It has been reported that T cells infiltrating salivary glands and interstitial regions in the kidney in the same patients have different T-cell receptor V_β chains.[31]

In conclusion, our study indicates that subclinical RTA may be a characteristic manifestation both in primary and secondary SS, along with the progression of immunologic dysfunction, when the illness seems to be indolent.

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