LATENT RENAL TUBULAR ACIDOSIS IN SJØGREN'S SYNDROME*

BY

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Renal tubular acidosis (RTA) is a syndrome characterized by hyperchloraemic acidosis and an inability to excrete a highly acid urine, in which impairment of acid excretion is out of proportion to reduction of glomerular filtration rate. RTA may occur in the absence of any associated disorder (primary RTA) or may coexist with a variety of disease states, including Wilson's disease, hyperthyroidism, pyelonephritis, multiple myeloma, galactosaemia, Lowe's syndrome, cystinosis, potassium deficiency, heavy metal poisoning, and the effects of nephrotoxic drugs (Huth, Mayock, and Kerr, 1959; Milne, 1963). Recently it has been observed after cadaver kidney homotransplantation (Massry, Preuss, Maher, and Schreiner, 1967). Subclinical or incomplete forms lacking the overt features of RTA also occur, and have been uncovered by means of an acid-loading test that detects an inadequate renal response to induced acidosis (Wrong and Davies, 1959; Huth, Webster, and Elkinton, 1960).

In the past few years, several reports have appeared indicating that RTA may be associated with Sjögren's syndrome (SS) (Shearn and Tu, 1965; Talal, 1966; Morris and Fudenberg, 1967). In view of these observations we attempted, by means of an acid-loading test, to detect latent RTA in ten patients with SS who lacked overt abnormalities of acid-base balance. Impairment of acid excretion consistent with RTA was found in three of the ten patients.

Material and Methods

The subjects were nine women and one man (mean age 44 years), each with a disorder that met the criteria for the diagnosis of SS, including at least two of the following

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three features:

- (1) Keratoconjunctivitis sicca;
- (2) Salivary gland enlargement or xerostomia;
- (3) Inflammatory joint disease.

All subjects were free from circulatory failure and arterial hypertension at the time of study. All had normal values for serum electrolytes, blood pH, and 24-hour endogenous creatinine clearance. None had hyperchloraemic acidosis.

The above determinations were also performed on 21 presumably normal members of the hospital's resident and general staffs, whose mean age did not differ significantly from that of the ten patients with SS ($P = 0.25$). In no patient or control did the bacterial count of a clean-voided, midstream morning urine specimen exceed 10^5 /ml. at the end of a 24-hour culture period.

The following tests were performed on each patient and control. A 24-hour urine specimen was tested for alpha amino nitrogen. Blood was drawn in the fasting state for the determination of serum potassium, chloride, carbon dioxide, sodium, calcium, and phosphorus. An acid-loading test according to the method of Wrong and Davies (1959) was then conducted:

Ammonium chloride powder in gelatin capsules (0.1 g./kg. body weight) was ingested over a 1-hour period. Urine was collected for 100 minutes before and at hourly intervals for 6 hours after the ingestion of ammonium chloride; pH was measured within 15 minutes, using a glass electrode in a Beckman pH meter; ammonium by the microdiffusion method of Conway (1947); titratable acid by titrating urine to pH 7.4 with N/50 sodium hydroxide. Before the ingestion of ammonium chloride and 2 to 4 hours thereafter, usually at times coinciding with minimal urine pH values, "arterialized" capillary blood ("finger stick" blood after warming hand in water at 45° C. for 10 minutes) was collected anaerobically and analysed for pH with a Radiometer at 37° C. The rates of titratable acid and ammonium excreted in urine after administration of ammonium chloride were calculated from the 5-hour collection between the beginning of the 2nd and the end of the 6th hour and expressed as $\mu\text{Eq.}/\text{min.}/1.73 \text{ M}^2$ body surface area.

To provide an estimate of renal concentrating ability, osmolality of a morning urine specimen after 14 hours' fluid restriction was determined by means of a Fiske osmometer.

Serum proteins were analysed by paper electrophoresis on a Spinco model R apparatus with an Analytrol reader. Total proteins were determined by the biuret method.

The mean values of data from patients and controls were compared by Student's *t*-test.

Results

The effect of ammonium chloride administration on acid excretion in the patients and the control subjects is summarized in the Table. A significant increase in concentration of blood hydrogen ion was observed in all subjects ($P < 0.025$). The degree of elevation of hydrogen ion concentration was similar in patients and controls ($P > 0.40$); yet renal acid excretion was considerably less in the patient group.

Three of the ten patients (1, 2, and 3) showed definite impairment of acidification of urine (Fig. 1); their individual pH values (5.45, 5.5, 5.52) substantially exceeded 5.19 (control group mean ± 2.58 S.D.). Excretion of titratable acid and ammonium by patients after ammonium chloride loading is also shown in Fig. 1.

Of the three patients with impaired acidification, the antinuclear antibody test was positive in two; it was also positive in all but two of the seven patients with normal acidification. The L.E. test was positive in only one (Patient 2) of the ten with Sjögren's syndrome; this was a woman in whom renal acidification was impaired.

In no patient was there an increase in urinary alpha amino nitrogen; nor was glycosuria, hypouricaemia, or hypophosphataemia observed.

Fig. 1.—Urinary pH, titratable acid, and ammonium (NH_4) response to oral administration of 0.1 g/kg. ammonium chloride (NH_4Cl) in three patients with Sjögren's syndrome and 21 controls; designation of two standard errors.

TABLE
RESULTS OF RENAL FUNCTION TESTS IN PATIENTS WITH SJÖGREN'S SYNDROME AND IN NORMAL SUBJECTS

Group	Patient No.	Age (yrs)	Sex	Creatinine Clearance (ml./min.)	Urine Osmolality after Thirsting (mOsmol/kg.)	Blood (H^+)		Minimal Urine pH	Titratable Acid ($\mu\text{Eq./min.}$)	NH_4 ($\mu\text{Eq./min.}$)	Serum γ Globulin (g./100 ml.)
						Before NH_4Cl (mEq./l.)	After NH_4Cl (mEq./l.)				
Sjögren's Syndrome	1	28	F	102	921	37.16	43.66	5.50	43.69	45.38	2.23
	2	41	F	79	814	—	—	5.45	24.77	22.47	1.58
	3	54	F	71	486	40.74	43.66	5.52	19.29	36.05	3.80
	4	25	F	80	800	44.67	63.10	4.60	30.43	30.61	1.45
	5	32	F	95	621	38.91	42.66	5.05	38.17	51.68	1.44
	6	36	M	116	1038	37.16	41.69	5.00	29.95	36.20	2.80
	7	48	F	98	770	45.71	47.87	5.00	27.82	37.36	2.42
	8	52	F	113	1000	42.66	51.29	4.70	59.53	34.26	1.38
	9	57	F	75	677	38.12	40.74	4.90	45.10	33.82	2.02
	10	70	F	88	400	34.68	41.69	4.90	31.21	45.29	1.17
	Means	44.0		91.00	752.7	39.98	46.26	5.06	35.00	37.31	2.03
	S.E.*	4.2		5.18	62.3	1.18	0.22	0.01	3.54	2.99	0.24
Normal Subjects	Means	38.4		110.01	958.0	39.65	42.00	4.81	51.70	50.76	1.08
	S.E.*	2.4		5.14	29.2	.55	.68	.03	3.45	3.23	.02†

*S.E. = Standard Error.

†Values derived in this laboratory from a separate group of 100 normal subjects.

The group mean of urine osmolality after fluid restriction in the normal subjects was 958.0 mOsm/kg., and in the SS group 752.7 mOsm/kg. ($P < 0.05$) (Fig. 2).

Fig. 2.—Osmolality of urine following 14 hours' fluid deprivation in ten patients with Sjögren's syndrome (SS) and in normal controls.

Discussion

An acute acid load as a test of renal acid excretion, especially for the detection of inapparent acidification defects, has been discussed at length by Wrong and Davies (1959). The application of such a stress test to detect occult or latent renal tubular acidosis resembles the use of a glucose tolerance test in early diabetes, where the fasting blood sugar is normal but a glucose load produces an abnormal response.

In none of the patients with SS herein studied was there overt evidence of renal tubular acidosis (hyperchloraemic acidosis) before ammonium chloride administration, suggesting that the renal

abnormality was mild enough to permit maintenance of normal acid-base balance when the acid load did not exceed the usual dietary and endogenous quantities of hydrogen ion. After blood acidity had been increased by ammonium chloride ingestion, three of the ten patients with SS exhibited an inability to lower urinary pH below 5.45 and to increase their rates of ammonium and titratable acid excretion as much as normal subjects. Such findings in these three patients are characteristic of the pattern of response to induced metabolic acidosis in patients with renal tubular acidosis, although in the overt syndrome the magnitude of the abnormality may be greater.

Because the creatinine clearance rates in these three patients (mean, 84 ml./min.) were slightly lower than in the controls (110 ml./min.), it might be argued that their inability to excrete a highly acid urine and their diminished rate of acid excretion were related to the glomerular filtration rate. That this is unlikely may be suggested by the following considerations. Patients with generalized renal failure without RTA maintain the ability to excrete a highly acid urine even in advanced disease and uraemia (Wrong and Davies, 1959). It is of interest that, when the rate of net acid excretion in our three patients with SS is considered per unit of creatinine clearance (mean, 75 μ Eq./min.), it is seen not to be increased, but actually to be low (101 μ Eq./min. in controls). This contrasts with the observation in generalized renal disease, where ammonium excretion per unit of glomerular filtration rate is increased when the absolute rate of ammonium excretion is low (Dorhout-Mees, Machado, Slatopolsky, Klahr, and Bricker, 1966). The increased rate of excretion per unit of glomerular filtration rate in generalized renal disease has been interpreted as a compensatory adaptation of the remaining intact nephron to reduction in functioning nephron mass (Dorhout and others, 1966). The impairment in ability to excrete hydrogen ion in our three patients appears, therefore, not to be entirely explained by reduction in the glomerular filtration rate.

In addition to the acidification defect, the patients with SS exhibited decreased renal concentrating ability. Impairment of urinary concentration in patients with SS was observed by Kahn, Merritt, Wohl, and Orloff (1962). Occasionally the abnormality is extreme, as in a patient reported from this laboratory (Shearn and Tu, 1965), who was totally unable to abstract solute-free water during sustained infusion of vasopressin. A concentrating defect of various degrees is frequently associated with RTA of both the primary and secondary types.

In the patients with SS studied here, most of the factors known to cause renal tubular dysfunction could be eliminated on the basis of their histories and laboratory findings. The age range of the patients with SS and RTA did not differ significantly from that of the normal subjects. Serum levels of potassium, sodium, and calcium were normal in each patient. Of the three patients with RTA, one took no drugs, another had taken between 5-10 mg. prednisone daily for 10 years, and the third had taken only salicylates, in doses of less than 2 g. daily. We do not know whether chronic administration of small doses of salicylates or prednisone will affect renal acid excretion, but it should be noted that such agents were also consumed by the patients with SS who had normal renal acidification. Although the chronic administration of analgesics has been implicated in the genesis of renal disease, Sørensen (1966), after studying more than 2,000 patients, recently concluded that the relationship between salicylates and renal disease is probably coincidental and not causal. We could not detect any abnormality in renal acidification after administering ammonium chloride to a group of eighteen patients with rheumatoid arthritis, most of whom were receiving more than 3 g. salicylates daily (Tu and Shearn, 1967a). These ten patients had not received other drugs that may induce RTA, such as tetracycline, amphotericin, or heavy metals.

Glycosuria, aminoaciduria, phosphaturia, or uricosuria (Fanconi's syndrome) may be associated with RTA (Burnett and Williams, 1958), but none of these was present in any of the patients herein studied. In the patients with SS and coexisting Fanconi's syndrome who have been reported (Clinicopathologic Conference, 1964; Shearn and Tu, 1965), extensive pathological changes including marked tubular atrophy and fibrosis were noted. Renal biopsy was performed in only two of our patients: Patient 10 was normal and Patient 4 revealed alterations in the interstitial zones but achieved the lowest urine pH (4.6) of the entire group after ammonium chloride loading. Not enough information is available regarding the histological changes in the kidney to justify relating the renal tubular functional defect to anatomic alterations.

The process that interferes with renal function in patients with SS has not been identified; however, the relationship between RTA and hypergammaglobulinaemia is of interest in this regard. Cohen and Way (1962) reported RTA in three patients with hyperglobulinaemic purpura; in one of their patients the hyperglobulinaemia preceded the acidosis by at

least 6 years. LoSpalluto, Dorward, Miller, and Ziff (1962) reported RTA in a patient with cryoglobulinaemia due to the interaction of an IgM with an IgG globulin. Recently, Wilson, Williams, and Tobian (1966) observed RTA in three patients with a symptom complex consisting of xerostomia, anaemia, and hepatosplenomegaly with quantitative abnormalities in serum IgA, IgG, and IgM; renal biopsy in one revealed no immunoglobulin deposition in glomeruli or tubules. In a more exhaustive study, Morris and Fudenberg (1967) noted renal acidification defects in hyperglobulinaemic states due to diverse causes, including two cases of SS; however, they could find no correlation between an increase in a specific serum immune globulin fraction and the occurrence of impaired renal acidification.

The serum gamma globulin concentration was raised not only in the three patients with SS and RTA in the present series, but also in most of those with SS and normal acidification. Similarly, in a recently studied group of patients with systemic lupus erythematosus, no clear relationship was observed between gamma globulin concentration and maximal urine acidification (Tu and Shearn, 1967b). No correlation was apparent ($P > 0.30$).

Fig. 3.—Serum gamma globulin concentration in patients with systemic lupus erythematosus (Tu and Shearn, 1967b) and Sjögren's syndrome plotted against minimal urine pH after ammonium chloride loading. No correlation exists ($P > 0.30$).

between serum gamma globulin concentration and minimal urine pH after ammonium chloride loading in the patients with systemic lupus erythematosus or in the subjects with SS in the present study (Fig. 3, opposite).

Recently, Massry and others (1967) reported the development of renal tubular acidosis in a patient who showed signs of graft rejection after having received a cadaver homotransplantation. Because the homograft rejection phenomenon has been clearly related to an immunological event, this aroused conjecture that an antigen-antibody reaction between the transplanted kidney and the recipient might have been responsible for the observed renal tubular dysfunction. The development of renal tubular acidosis during the course of SS raises similar questions, since speculation that inappropriate immunological mechanisms may be operative in this disease has been stimulated by some of its features such as abnormal levels of immunoglobulins, and the presence in the blood of antibodies that react with tissue components (Bloch, Buchanan, Wohl, and Bunim, 1965). Attractive

though this may be as a hypothesis, no presently available information links the renal tubular defect observed in Sjögren's syndrome to a known underlying immunological abnormality.

Summary

In ten nonazotaemic patients with Sjögren's syndrome, renal acidification and concentration were evaluated and compared with those in 21 normal subjects. Although no overt acid-base imbalance was present in any subject, in three patients the renal response to the administration of an acute acid load was inadequate, and renal concentrating capacity was slightly impaired. These findings are consistent with latent renal tubular acidosis. Thus, it appears that renal tubular acidosis, the detection of which may be facilitated by an acid loading test, may be an occasional feature of Sjögren's syndrome.

The cause of renal tubular acidosis and its possible relationship to hypergammaglobulinaemia are discussed.

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L'acidose rénale latente d'origine tubulaire au cours du syndrome de Sjögren

RÉSUMÉ

L'acidification et la concentration rénales furent évaluées chez dix malades non azotémiques ayant un syndrome de Sjögren et on compara les résultats avec ceux de 21 témoins. Bien qu'il n'y eut de déséquilibre acide-base apparent chez aucun sujet, chez trois malades la réponse rénale à une surcharge acide importante fut insuffisante et la capacité du rein à concentrer fut légèrement diminuée. Ces résultats s'accordent avec l'existence d'une acidose rénale tubulaire latente. Ainsi il apparaît que l'acidose tubulaire rénale dont la détection peut être rendue plus facile par le test de surcharge acide, peut être une manifestation occasionnelle du syndrome de Sjögren.

On discute la cause de l'acidose tubulaire rénale et son rapport possible avec l'hypergammaglobulinémie.

Acidosis tubular renal latente en el síndrome de Sjögren

SUMARIO

Se valoraron la acidificación y la concentración renales en diez enfermos no azotémicos con síndrome de Sjögren y se compararon los resultados con los obtenidos en 21 testigos. En ningún sujeto se observó un desequilibrio ácido-base aparente, pero en tres enfermos la respuesta renal a la administración de una sobrecarga de ácido fue inadecuada y la capacidad renal de concentración algo disminuida. Estos resultados son compatibles con la existencia de una acidosis tubular renal latente. Así pues, la acidosis tubular renal, cuya detección facilita un test de sobrecarga ácida, puede constituir a veces un rasgo del síndrome de Sjögren.

Se discute la causa de la acidosis tubular renal y su relación posible con la hipergammaglobulinemia.