DISTAL TUBULAR DYSFUNCTION WITH RENAL CALCIFICATION*

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Since the initial description by Albright *et al.*[3] of the syndrome of diffuse renal calcification associated with changes in renal function, other similar cases have been reported.[1, 2, 4, 5, 6, 11, 18, 19] Metabolic balance studies[1, 2] have demonstrated that the altered renal function in this disease usually consists of an inability of the kidney to exchange hydrogen and ammonium ions for sodium so that the loss of sodium from the body in relation to chloride loss is excessive, and metabolic acidosis results. There is also an associated inability of the kidney to conserve water despite systemic dehydration. Both of these functions—the elaboration of an acid urine and ammonia and the facultative reabsorption of water—are considered to be distal tubular functions.[15, 16, 17, 20, 21]

This case is reported because the history possibly suggests congenital origin of this disturbance. The procedures which were carried out in arriving at a definitive diagnosis may be of some interest.

Case history

R.A.† was admitted for the first time to the Pediatric Service of the New Haven Hospital in February, 1950, at the age of six years, with a provisional diagnosis of primary hyperparathyroidism. The chief complaint was that of failure to grow.

Family history. Both parents were of low normal stature. A female sibling had pyloric stenosis in infancy which was relieved by pyloromyotomy.

Past history. The prenatal course of this child was uneventful. His delivery was spontaneous and normal at full term. The birth weight was seven pounds and one-fourth of an ounce. There was frequent vomiting until nine months of age attributed to pylorospasm; weight gain was slow during that time. The weight at one year was fifteen pounds and there was an acceleration of the weight gain at eighteen months. The intake of vitamins C, D, and A was adequate but at no time excessive.

Present illness. The history relevant to the present illness began almost at birth. During the first few months of life it was noted that the child consumed as much as eight ounces of water between each feeding. This polydipsia continued until admission at which time the water intake was about eight to ten glasses per day in addition to one and one-half quarts of milk. Nocturia of two times per night had been present since toilet training had been begun. Because of albuminuria and retarded growth noted in a routine school physical examination, he was admitted to a neighboring hospital. There, a urine concentration test revealed a specific gravity fixed below 1.010. The serum calcium was said to be 15.0 mg. per 100 cc. The alkaline phosphatase was

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6.0 Bodansky units. Roentgenographic examination of the abdomen revealed a marked, diffuse speckled calcification of both kidneys. The intravenous pyelogram revealed normal excretory function with no evidence of obstruction in the urinary tract. Urine cultures were negative. Because of these findings the patient was referred to this department.

Physical examination. The patient was a small, fairly well nourished, reddish haired, white boy who was alert and intelligent. The body weight was 15 kg. and the height was 45¾ inches. The size of this child was that of an average child aged four years and eight months.* The vital signs including blood pressure were normal. There were no other abnormal physical findings except for a Grade I precordial systolic murmur which was considered to be functional and *pes planus* right with moderately severe pronation. The skin was somewhat dry. There were no palpable masses nor enlarged organs in the abdomen.

TABLE 1

SERUM ANALYSES

Date	NPN *mg.%*	CO_2 *mEq./l.*	Cl *mEq./l.*	Na *mEq./l.*	K *mEq./l.*	Ca *mg.%*	P *mg.%*	*Alb. gm.*	*Glob. gm.*	*pH*
March										
1	41	11	112	140	4.7	10.6	4.1	4.3	3.7	
8	40	16	106	137	4.5	11.1	4.8	4.3	3.1	7.32
13	45	16	109	139	4.3	10.2	5.8			
14						10.7				
18	35	25	98	143	4.1	10.0	5.0			
21		25				10.9				

TABLE 2

PLAN OF BALANCE STUDY

Procedure	*Period*			
	I	II	III	IV
Duration, days	5	2	3	3
Diet	Control	Control	Control	Control
Parathyroid extract		50 U. every 16 hrs. i.v.		
Sodium citrate			90 mEq./day	
Sodium acetate				90 mEq./day

Roentgenographic findings. Radiographs of the skull and extremities showed no evidence of osteoporosis or osteitis fibrosa. Dental radiographs revealed no changes in the lamina dura. There was delayed appearance of the centers of ossification of both wrists with no appearance of the centers which are usually present at the age of five years. The kidney shadows were normal in size, shape, and position. There

* The plotting of this data on a Wetzel growth chart indicated that he was in channel A_1 with an isodevelopmental line of 10, placing him in an auxodrome in which ninety-eight per cent of the children of his own age are larger than he and in which sixty-seven per cent of children of age four years and eight months are found.

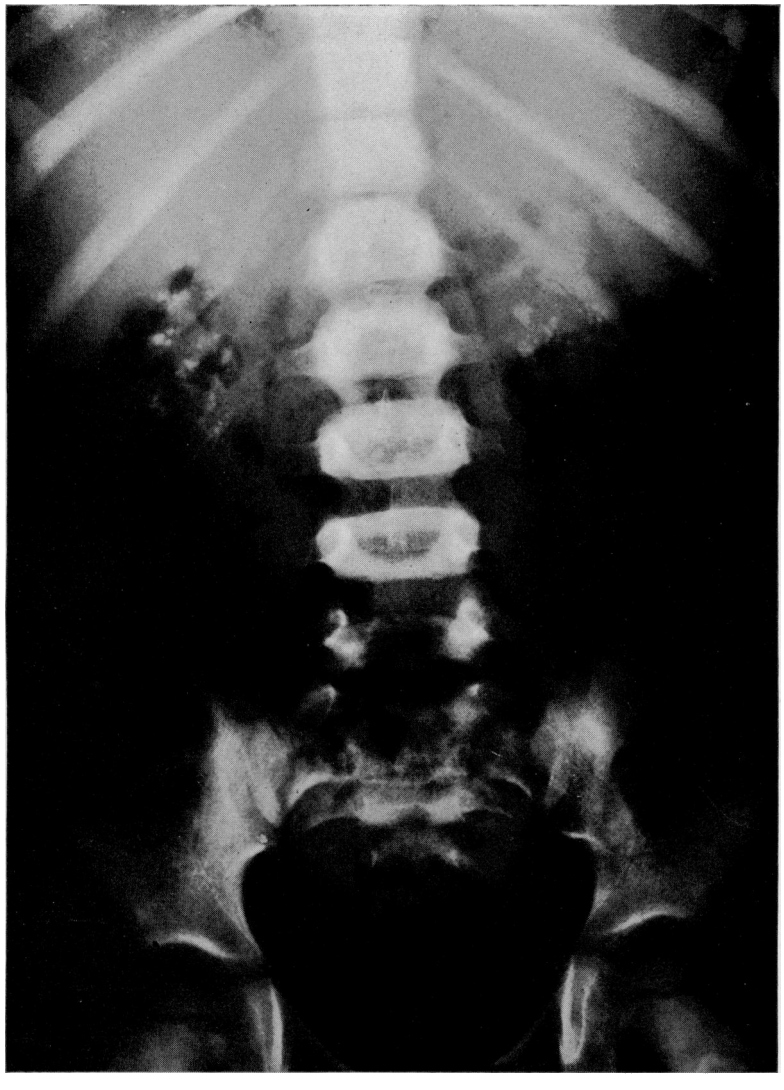

FIG. 1. Radiograph showing marked diffuse bilateral calcification of the renal parenchyma.

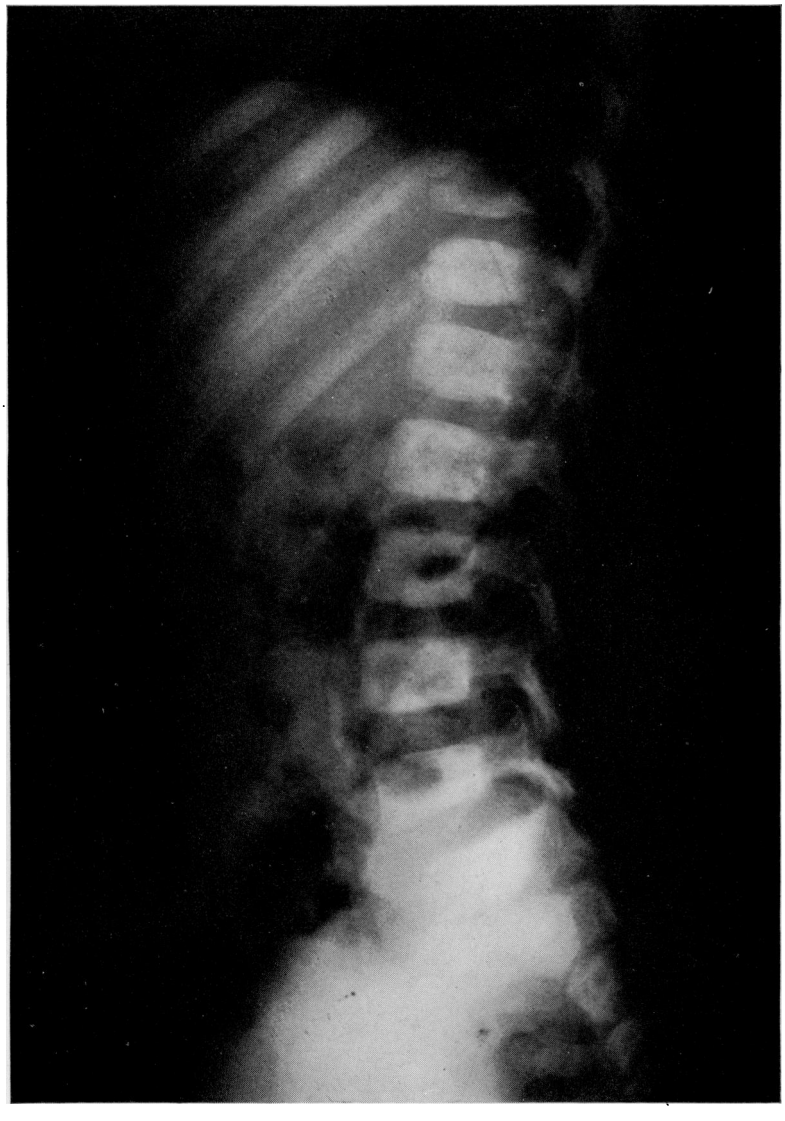

FIG. 2. Lateral view of the abdomen showing renal calcification.

was marked focal calcification speckled throughout the kidneys bilaterally with a preponderance in the medullary region. (Figs. 1 and 2.)

Laboratory data. Urinalysis revealed a specific gravity of less than 1.010 despite restriction of fluids for eighteen hours. There was a trace of albumin in the urine. Occasional white blood cells were noted in the urinary sediment. There were no reducing substances in the urine. Qualitative tests for cystine were negative. The Sulkowitz test for calcium in the urine was equivocal. The urine pH was never below 6.8. A phenolsulfonephthalein excretion test revealed ten per cent excretion in fifteen

TABLE 3

BALANCE DATA

Period	*Total weight gm.*	*Water gm.*	*Fat gm.*	N *gm.*	Cl *mM.*	Na *mM.*	K *mM.*	P *mM.*	Ca *mM.*	NH_3 *mM.*	*Tit. acid mM.*	*pH*
I												
5 D.												
Urine	8362			36.3	283	221	341	130	25	85	17	7.0
Stools	336	252	22	4.1	5	1	35	85	166			
Intake	16351	14887	179	63.5	344	258	465	235	204			
Balance	7653		157	23.1	56	36	89	20	13			
II												
2 D.												
Urine	3539			16.9	126	107	135	54	11	34	31	6.8
Stools	127	94	9	1.7	1	1	14	39	70			
Intake	5635	5050	71	26.2	126	94	185	96	83			
Balance	1969		62	7.6	—1	—13	36	3	2			
III												
3 D.												
Urine	4932			21.6	161	251	140	60	9	24	0	7.6
Stools	150	112	11	1.9	1	1	21	45	65			
Intake	8718	7957	90	29.7	173	433	250	114	99			
Balance	3636		79	6.3	10	181	89	9	25			
IV												
3 D.												
Urine	5763			21.9	207	432	200	74	8	7	0	7.6
Stools	245	194	12	2.5	3	3	24	41	78			
Intake	10417	9469	122	38.5	225	452	306	141	124			
Balance	4409		110	14.1	15	17	82	26	38			

minutes and sixty-two per cent in two hours. The hemogram was essentially normal except for a hemoglobin of 12.5 grams per 100 cc. which rose to 14.0 grams during the urine concentration test. The tuberculin test was negative, as were cultures of the blood and urine and serological examination for syphilis.

The analysis of serum on admission revealed a marked metabolic acidosis with hyperchloremia (Table 1). A metabolic balance study was performed to determine the nature of this electrolyte disturbance, using techniques previously described;[8] it consisted of four experimental periods (Table 2).

Results of the balance study

During the five-day control period the presence of hypercalciuria was demonstrated (Table 3). The renal excretion of calcium was 5.0 mM. per day, at least twice the high normal excretion.[18] The retention of chloride exceeded the retention of sodium despite the presence of severe metabolic acidosis (Table 1). The reason for this finding was obvious from the insignificant ammonia and titratable acid production during the period (84.6 and 16.7 mEq., respectively).

In the second period, parathyroid extract was administered intravenously three times without any marked change in the overall electrolyte balance from the control period, despite the immediate change in phosphorus excretion described below.

TABLE 4
PARATHYROID EXTRACT STIMULATION

Time	P *mM./hour*	Ca *mM./hour*	Na *mM./hour*	K *mM./hour*	Cl *mM./hour*
Pre—					
1 h	.836	.147	2.4	2.7	3.1
2 h	.838	.162	1.7	3.6	3.1
3 h	.916	.181	1.8	3.7	3.1
4 h	.965	.160	1.6	3.3	2.4
*Post—					
1 h	1.398	.227	3.3	2.5	3.9
2 h	1.616	.176	2.4	2.5	2.9
3 h	1.577	.197	2.5	2.2	3.0
4 h	1.496	.257	2.2	4.4	3.0
5 h	1.432	.253	2.9	3.3	2.8

*0.5 cc. Parathyroid Extract i.v. (50 units USP).

With the administration of sodium citrate, 90 mEq. per day (Period III), sodium was retained in excess of chloride with a rise in serum carbon dioxide content to 25.0 mEq. per liter. Concomitantly, there was a fall in calciuria to high normal levels. With continuation of alkali therapy (Period IV) the sodium retention fell to that of the chloride retention. Calcium excretion by way of the urine was reduced even further to 2.5 mM. per day. The retention of calcium and phosphorus per day was significantly increased above the control period. The retention of calcium increased from 2.6 mM. per day in the control period to 12.8 mM. on alkali therapy, and the retention of phosphorus increased from 3.9 mM. per day to 8.7 mM.

In an attempt to demonstrate the acute effect of parathyroid extract on renal phosphorus excretion, hourly urines were studied after administration of fifty units of the extract. These showed a significant increase in the renal excretion of phosphorus above the control values (Table 4). Within one

hour after the administration there was a rise in the hourly phosphorus excretion to somewhat less than double the control values. The excretion of phosphorus per hour in the control periods was about 0.89 mM., rose to 1.40 mM. within one hour, and reached a maximum of 1.6 mM. about two hours after the injection of parathyroid extract.

Pitressin hydrochloride (0.5 cc.) was administered intramuscularly at the end of the balance study and the urine volume and specific gravity were measured during a period of controlled water intake. There was no decrease in the hourly rate of urine formation nor increase in urine specific gravity after the injection of antidiuretic substance (Table 5).

TABLE 5

POSTERIOR PITUITARY EXTRACT STIMULATION

Time	*Urine gm.*	*Specific gravity*	*Intake cc.*
Pre—			
1 h	61	1.003	60
2 h	59	1.003	60
3 h	61	1.000	60
*Post—			
1 h	72	1.004	60
2 h	67	1.004	60
3 h	74	1.004	60
4 h	42	1.004	60

* 0.5 cc. Pitressin i.m.

Discussion

Before the balance study was performed there seemed to be two diagnostic possibilities. First, the renal calcification might represent a pathological reaction to an old renal injury, such as infection, without progression. Second, this calcification might be progressively increasing because of enhanced renal excretion of calcium. This hypercalciuria could be due to primary hyperparathyroidism or chronic acidosis.

The control period of the balance study definitely established the presence of excessive calcium excretion by way of the urine. This excretion was at least twice the high normal renal excretion of calcium. Furthermore, in this control period it was noted that the production of ammonia and titratable acid was grossly deficient despite the stimulus of a severe systemic metabolic acidosis. This deficient exchange of ammonium and hydrogen ions for sodium prevented the reabsorption of sodium in excess of chloride which would have normally occurred to correct the metabolic acidosis. There was no demonstrable disturbance in potassium metabolism in contrast to the finding of Albright in some of his cases.[1,2] There was adequate

retention of potassium in relation to nitrogen, and hypokaliemia was not observed.

The experiment in which parathyroid extract was administered was carried out in an attempt to rule out primary hyperparathyroidism as the cause of the renal calcification.

The diagnosis of primary hyperparathyroidism is untenable in the presence of repeated normal or high normal serum inorganic phosphorus concentrations unless the renal excretion of phosphorus is impaired. In this case the response to parathyroid extract was similar to that of normal subjects studied by Ellsworth and Howard[10] and by others.[12] In patient R.A. there was a marked increase in the renal excretion of phosphorus within one hour after the administration of parathyroid extract, and this response indicated that the renal pathway for phosphorus excretion was not impaired, and the kidneys could respond to parathyroid hormone stimulation. Consequently, the high normal concentration of inorganic phosphorus in the serum of this patient made the diagnosis of primary hyperparathyroidism unlikely. The renal phosphorus excretion for the whole of Period II was essentially the same as in the control period, despite the intravenous administration of parathyroid extract three times during Period II. This finding is not in conflict with the results of the parathyroid stimulation experiment noted above. The intravenous administration of parathyroid extract produces an immediate increase in phosphorus excretion which may fall to less than control levels of excretion several hours after administration.[7] This negative rebound might explain our findings in Period II of the balance study.

The inability of the end organ—the renal tubule—to respond to antidiuretic substance which was injected further indicates a distal tubular dysfunction as the basis for the obligatory polyuria. The etiology of the tubular dysfunction is not clear. The onset of polydipsia in infancy without other signs or symptoms of acute or chronic renal disease is suggestive of a congenital defect in the enzyme structure of the cells of the distal convoluted tubules of the kidneys with calcification resulting from long maintained hypercalciuria secondary to chronic metabolic acidosis. However, the presence of calcification may not be essential in this syndrome,[9,11] and secondary renal injury may be avoided if calcification can be prevented. The early diagnosis of this condition would seem to be essential for the prevention of irreversible renal injury by preventing hypercalciuria.

The results of the balance study carried out during the administration of sodium citrate and sodium acetate indicate that by reduction in calciuria renal calcification might be prevented. The mechanism of the reduction in calciuria following alkalinization is not understood at the present time. It has been postulated that the correction of acidosis reduced the concentration of filterable calcium in the serum and thereby reduced the amount of calcium filtered. This explanation is probably unlikely in view of the work

of McLean and Hastings[14] and Dillman and Visscher,[9] since the pH of the serum was not particularly low (pH 7.32) before alkalinization. If a cation exchange system were involved in the distal tubule, the increased sodium reabsorption during alkali therapy might displace calcium inward from the tubular cell and thereby prevent calcification and calciuria. The actual mechanism involved in the reabsorption and excretion of calcium remains to be worked out. Sodium citrate did not seem to be superior to sodium acetate in decreasing the hypercalciuria.

The fairly large positive balances of nitrogen, calcium, and phosphorus suggest that the growth rate of this child may be accelerated by this therapy. These assumptions are confirmed somewhat by the examination of the patient two months after discharge during which period 90 mEq. of sodium acetate were taken daily. At that time were noted a weight gain of eight pounds, which did not seem to be due to sodium retention, as well as an increase in height of one-half inch and a rise of the serum alkaline phosphatase to 18 Bodansky units. The latter probably represents increased osteoblastic activity in the bones.

Summary

A case of distal tubular dysfunction with renal calcification of possible congenital origin is reported. The laboratory procedures which were necessary to confirm the diagnosis are described. The administration of parathyroid extract was used as a means of ruling out primary hyperparathyroidism.

Addendum

Since this paper was submitted for publication, radiographic study of the 4-year-old female sibling was performed. Extensive speckled calcification of both kidneys was noted. Further study of this family will be reported subsequently.

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