Decreased Bicarbonate Threshold and Renal Magnesium Wasting in a Sibship With Distal Renal Tubular Acidosis

(Evaluation of the Pathophysiologic Role of Parathyroid Hormone)

By Michael F. Michelis, Allan L. Drash, Louie G. Linarelli, Frederick R. De Rubertis, and Bernard B. Davis

Two siblings with impaired distal renal tubular acidification and nephrocalcinosis associated with vasopressin-resistant polyuria are described. They also exhibit decreased renal bicarbonate threshold and defective renal magnesium conservation with a concomitant hypomagnesemia. Evaluation of other family member revealed no such abnormalities. Parathyroid hormone (PTH) has been shown to affect the renal tubular handling of both bicarbonate and magnesium. The role of the hormone in the development of the observed abnormalities of excretion of these substances was evaluated in both siblings. Following initial determinations, which in the older child suggested increased PTH effect, studies were performed on the two siblings to assess levels of PTH secretion both by indirect methods and by direct immunoassay of their sera. The results indicated excessive PTH secretion in the older sibling, but not in the younger. It was concluded that increased PTH secretion was not responsible either for the abnormalities of bicarbonate excretion or for the excessive urinary magnesium losses demonstrated in the two siblings. Further, neither vitamin D resistance nor secondary hyperparathyroidism appears necessary for the development of nephrocalcinosis in such disorders. Finally, responses to therapy indicate that the acidosis in both siblings was corrected, as expected, by alkali administration, but the hypomagnesemia did not correct (due to increased urinary losses) with either oral on parenteral magnesium supplements.

RENAL TUBULAR ACIDOSIS (RTA) is the designation given to a group of disorders currently regarded as resulting either from an abnormality of the proximal tubule (proximal RTA) characterized by defective reabsorption of bicarbonate there, or from a distal tubular abnormality (distal RTA) in

From the University of Pittsburgh School of Medicine, Pittsburgh, Pa.

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Michael F. Michelis, M.D.: *Assistant Professor of Medicine, University of Pittsburgh School of Medicine; and Chief, Renal Diagnostic Unit, V. A. Hospital, Pittsburgh, Pa.* Allan L. Drash, M.D.: *Associate Professor of Pediatrics, University of Pittsburgh School of Medicine; and Director, Clinical Study Center, Childrens Hospital of Pittsburgh, Pittsburgh, Pa.* Louie G. Linarelli, M.D.: *Clinical Assistant Professor of Pediatrics, University of Pittsburgh School of Medicine; and Chairman, Pediatrics Department, Mercy Hospital, Pittsburgh, Pa.* Frederick R. DeRubertis, M.D.: *Fellow in Endocrinology, University of Pittsburgh School of Medicine, Pittsburgh, Pa.; present address, Physical Science Division, USAMRIDD, Fort Dettrick, Frederick, Md.* Bernard B. Davis, M.D.: *Associate Professor of Medicine, University of Pittsburgh School of Medicine; and Chief of Staff, V. A. Hospital, Pittsburgh, Pa.*

which secretion of hydrogen ion into the distal tubular fluid is impaired.[1] Distal renal tubular acidosis has been widely recognized since the descriptions of Lightwood[2] and Butler et al.[3] over 30 yr ago, while disorders of proximal tubular bicarbonate handling have been reported with increasing frequency only during the last decade.[4–6]

The present studies were performed on two siblings with impaired dis tubular hydrogen ion excretion and nephrocalcinosis, who also evidenced proximal tubular bicarbonate wasting and defective renal magnesium conservation. One sibling was hypocalcemic and had a vitamin D-resistant defect in gastrointestinal calcium absorption, while the other had normal calcium absorption and was normocalcemic.

Parathyroid hormone (PTH) is known to affect several renal tubular functions in addition to its well-known action of increasing phosphate excretion. For example, its proximal tubular effects include the ability to increase renal bicarbonate excretion.[7,8] PTH excess, as in primary hyperparathyroidism, has also been associated with decreases in distal tubular hydrogen ion secretory capacity,[9–11] but probably only when intrarenal calcification accompanies that disorder. The hormone, in addition, has an effect on renal magnesium handling. While acute parathyroid extract (PTE) administration results in renal conservation of magnesium,[12,13] chronic PTE administration increases renal magnesium loss.[13,14] Furthermore, patients with primary hyperparathyroidism have been observed to have decreased serum magnesium levels and excessive urinary losses.[15,16]

Since elevated levels of PTH secretion were suspected in one of the affected siblings, it was felt that they presented a unique opportunity to carry out studies to assess the possible role of PTH in the development of the urinary abnormalities noted in the two affected individuals. The patients' siblings and the one parent available for study were also evaluated. The results suggest that excessive PTH secretion was not related to the observed renal wasting of bicarbonate and magnesium.

CASE REPORTS

Patient 1

K.B., female, age 10, presented with complaints of bone pain, lethargy, and weakness on February 25, 1970, her initial admission to the Children's Hospital of Pittsburgh.

The patient's mother stated that the child was born at 34–35 wk gestation and had "jaundice" at birth, but was sent home 3 days later apparently in good health. At 2 yr of age, the girl was noted by the parent to develop polyuria and polydypsia, which has been present since. Later that year (1962), the patient was hospitalized for an acute urinary tract infection. Serum electrolytes were normal, cultures of the urine yielded a significant growth of *E. Coli*, and abdominal x-rays revealed bilateral diffuse nephrocalcinosis. The patient's infection responded favorably to antibiotic therapy prior to discharge.

Six months later the patient was again hospitalized for treatment of a urinary tract infection. During this admission, evaluation included cystoscopy and bilateral ureteral catheterization. No evidence of obstruction was found, and cultures from both ureters were sterile. The only positive finding was described as mild chronic inflammation of the trigone.

The patient apparently did well except for the persistence of polyuria and polydypsia

until 1966 when, at age 6, she was hospitalized following the development of a convulsive disorder described by the parent as "trembling all over." Neurologic examination, skull x-rays, and spinal tap demonstrated no abnormalities; an electroencephalogram, however, was read as "dysarrythmia, grade III, right temporal area." During this admission, serum calcium was recorded at 9.7 mg/100 ml, phosphorus 3.9 mg/100 ml, and serum alkaline phosphatase 12.6 Bodansky units (normal 5–14). Discharged with a diagnosis of idiopathic seizure disorder, the patient was begun on combined therapy of diphenylhydantoin, phenobarbital, and primidone.

In 1968 the patient was again hospitalized because of an increase in seizure activity. Laboratory data included: serum creatinine 1.0 mg/100 ml, urea nitrogen 25 mg/100 ml, calcium 7.7 mg/100 ml, phosphorus 4.3 mg/100 ml, and alkaline phosphatase 21.2 Bodansky units. Oxalate excretion was 17 mg/24 hr (normal is <39 mg/24 hr).

In early 1969 there occurred another hospitalization during which the complaint of bone pain was elicited and a urinary tract infection was again treated. The patient was discharged on primidone, diphenylhydantoin, nitrofurantoin, calcium gluconate, and acetazolamide. The latter was later discontinued. Her course prior to admission to this hospital was one of increasing exercise intolerance, bone pain, and weakness.

Physical examination of K. B. on admission here revealed normal temperature, pulse, and respiratory rate. Blood pressure was 100/70. Height was 126 cm (third percentile), and weight was 25 kg (third percentile). The examination demonstrated no abnormalities except for the suggestion of tibial bowing and dry skin of rough texture. Laboratory evaluation revealed Hgb 11.0 g/100 ml, normal WBC, differential and platelet count. Serum electrolytes were in the following ranges: serum sodium 135–146 meq/liter, chloride 109–120 meq/liter, potassium 3.9–4.3 meq/liter, bicarbonate 18–20 mmole/liter, calcium 5.9–6.5 mg/100 ml, phosphorus 3.2–4.6 mg/100 ml, magnesium 1.2 meq/liter, Alkaline phosphatase was 12.8 Bessey–Lowry units (normal 2.8–6.7), creatinine 1.27 mg/100 ml, urea nitrogen 26 mg/100 ml, fasting glucose 84 mg/100 ml; serum protein electrophoresis was normal. Twenty-four-hour urine collection examined for inborn errors including determination of glucose and chromatography for amino acids revealed no abnormality. The urine culture again was positive for a significant number of *E. Coli.* An electrocardiogram was normal.

Bone marrow examination was normal including the absence of crystalline inclusions. X-rays of the skull, thorax, abdomen, and extremities revealed the following findings: No lamina dura was seen, changes characteristic of active rickets were described in the hands and knees, nephrocalcinosis was documented (Fig. 1) and the bone age was interpreted as 3 SDs below the normal for this age group. The electroencephalogram was interpreted as consistent with epileptogenic activity with suggestive localization in the right hemisphere. Determinations of urinary pH, concentrating ability, and special studies are described later.

Patient 2

E. B., a male sibling, age 6, was also admitted to the Clinical Study Unit of the Children's Hospital of Pittsburgh for evaluation.

The patient was born after 33 wk gestation and birth weight was 5/6. He had a right inguinal herniorrhaphy and urethral meatotomy at 6 wk of age, at which time he was also treated for urinary tract infection. He has had no symptoms or laboratory evidence of urinary infection since. He has had polyuria and polydypsia since approximately 1 yr of age with nocturia 2 or 3 times nightly. There is no history of bone pain.

Physical examination revealed an asthenic male child who appeared small for his age. Vital signs were normal. Height was 105 cm (third percentile), and weight was 16.0 kg (third percentile). Remainder of the examination was normal. Laboratory data: Hgb 14.9 g/100 ml, WBC 7400. Culture of urine and urethral meatus was negative. Serum sodium 141 meq/liter, chloride 105 meq/liter, potassium 4.4 meq/liter, bicarbonate 22 mmole/liter, calcium 9.6 mg/100 ml, phosphorus 4.6 mg/100 ml, magnesium 1.1 meq/liter, alkaline phosphatase 5.7 Bessey–Lowry units, creatinine 0.7 mg/100 ml,

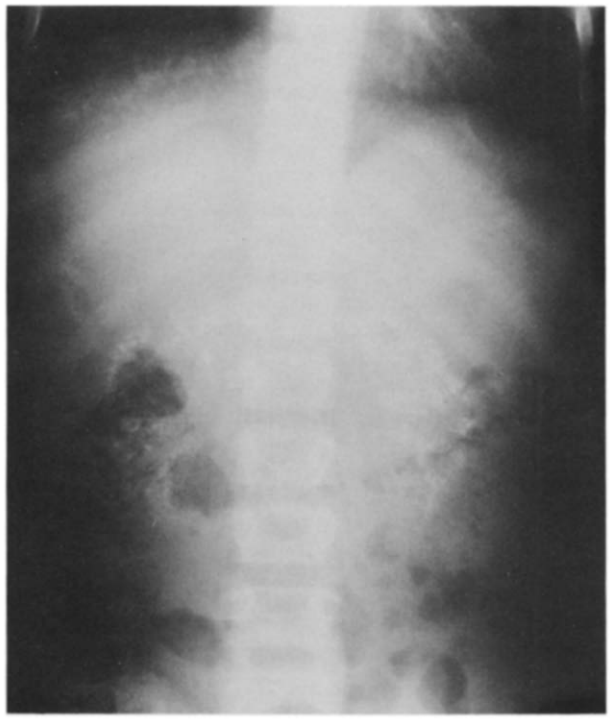

Fig. 1. Abdominal x-ray of patient K.B. demonstrating diffuse bilateral nephrocalcinosis. Findings in the younger sibling, E.B., were similar.

urea nitrogen 20.9 mg/100 ml, and total protein 7.9 g/100 ml, albumin 4.3 g/100 ml. Twenty-four-hour urine for amino acids, glucose, and inborn errors screening revealed no abnormality. Radiologic evaluation including x-rays of the skull, extremities, and thoracolumbar areas revealed only diffuse calcification of both kidneys and a bone age in the hand interpreted as 3 SDs below the normal for this age group. Measurements of urine pH, concentrating ability, and special studies are described later.

Family History

The mother disclosed that her husband, who is separated from the family and unavailable for evaluation, has ulcer disease, "arthritis," and asthma. He reportedly had normal kidney x-rays 2 yr ago. The mother also has ulcer disease and has a history of seven spontaneous abortions, the last one resulting in a hysterectomy. In addition to the two siblings described above, there are three other children all free of chronic disease. The oldest, however, has a history of urinary tract infection.

All five siblings and the mother were screened on the clinical study unit as described later. In addition, the two affected siblings, and an unaffected one serving as a control, were the subjects of more extensive evaluation.

MATERIALS AND METHODS

Family Evaluation

Initial studies on the five siblings and the available parent (mother) included determinations of serum sodium, chloride, potassium, bicarbonate, calcium, phosphorus, magnesium, alkaline phosphatase, creatinine, and urea nitrogen. X-rays of the abdomen were obtained, and routine urine analysis and urine culture were performed. Twenty-four-hour urine was obtained for glucose and amino acids.

Acid Loading

The six family members all received a standardized acid load. They were permitted a light breakfast, and pH and total CO_2 (tCO_2) were determined on arterialized capillary blood and a control 1-hr urine. An acid load of ammonium chloride, given as the liquid, was administered at a dose of 150 meq/sq m of body surface. Arterialized capillary bloods were then obtained 1 or 2 times several hours after drug administration to ensure the systemic effect. Hourly urines, voided directly into receptacles containing mineral oil with complete bladder emptying encouraged, were collected for 6 hr following ammonium chloride loading.

Control Observations

When the results of initial studies suggested that the only affected siblings were K.B. and E.B., both children were further evaluated. The oldest sibling, D.B., age 13, was also hospitalized for evaluation of a history of urinary tract infection. Following initial studies including intravenous pyelogram, all of which were normal, she participated as a control in some of the studies performed on the affected siblings. The three children were placed on ad lib. fluids and diets containing known daily amounts of calcium, phosphorus, and magnesium as follows: K.B.—calcium, 1.2 g, phosphorus, 1.2 g, and magnesium 250 mg; E.B. and D.B. both received diets of calcium, 500 mg, phosphorus, 900 mg, and magnesium, 250 mg. Returned portions of food were subtracted from daily totals. For 10 days daily fluid intake and 24-hr-urine volumes were quantitated and daily blood and urine specimens were measured for sodium, potassium, chloride, creatinine, calcium, phosphorus, and magnesium. Erythrocyte (RBC) magnesium levels were also determined. Per cent tubular reabsorption of phosphorus (%TRP) was calculated.

Calcium Absorption Studies

Gastrointestinal absorption of radioactive calcium was evaluated in K.B. and E.B. according to the method of Avioli et al.[17] The patients were given oral doses of labeled ^{47}Ca following which four 15-min and then hourly blood samples were obtained and radioactivity was measured. Urine was also collected and studied following administration of the radiocalcium.

Bicarbonate Infusion

The response to bicarbonate infusion was evaluated in the two patients and the older sister (D.B.), who was free of disease. Ammonium chloride was administered (75 meq/sq m) to decrease preinfusion serum bicarbonate levels (mean preinfusion level 14.3 mmole/liter) so that the bicarbonate threshold might more easily be characterized. Since the female patient K.B. had a seizure disorder and hypocalcemia, it was decided not to attempt measurement of the maximal rate of bicarbonate absorption (T_m) and infusions were terminated with serum bicarbonate at only mildly elevated levels (mean 27.2 mmole/liter). In spite of this precaution, however, the patient K.B. was observed to have several seizures during the later part of the study day, suggesting a possible untoward effect of performing this procedure in patients wtih underlying seizure disorders, hypocalcemia, or both.

The studies were performed with infusions that contained 15.0–22.5 g $NaHCO_3$/liter of fluid. The infusions were begun at a rate of 1.0 ml/min and the rate of infusion or concentration of infused bicarbonate was varied to effect desired serum bicarbonate response. Urine was collected at 30-min intervals, and midpoint venous and arterialized capillary blood samples were obtained. The patients were encouraged to empty their bladders completely and urine was collected directly under mineral oil. Determinations on the blood and urine samples included pH, tCO_2, sodium, potassium, chloride, calcium, phosphorus and creatinine, and pCO_2. Bicarbonate levels were calculated from the Henderson-Hasselbalch equation in the standard manner.[18]

Table 1. Initial Family Evaluation

		Blood (Serum)										Urine		X-Ray
Patient	Age (yr)	Na (meq/liter)	Cl (meq/liter)	K (meq/liter)	HCO_3 (mmole/liter)	Ca mg/100 ml	PO_4 mg/100 ml	Mg (meq/liter)	Alk. Phos. Bessey-Lowry U	Creat. mg/100 ml	BUN mg 100 ml	Culture	Glucose plus Amino Acids	Nephrocalcinosis
K.B.	10	138	112	4.0	19	6.0	3.5	1.2	12.8	1.2	26	+	—	+
E.B.	6	141	105	4.4	22	9.6	4.6	1.1	5.7	0.7	21	—	—	+
D.B.	13	138	101	4.0	24	9.4	5.2	1.9	7.8	0.9	11	—	—	—
C.B.	11	137	99	4.6	26	9.2	5.1	1.9	8.1	0.7	6.5	—	—	—
R.B.	8	139	97	4.0	25	9.4	4.8	1.8	8.3	0.8	9.1	—	—	—
J.B.*	33	141	100	4.1	24	9.8	4.2	2.0	8.1	1.1	17	—	—	—

* Mother.

Evaluation of Endogenous PTH Secretion

Since initial determinations (low serum phosphorus, increased alkaline phosphatase, low %TRP, and radiographic changes) in patient K.B. suggested increased PTH effect, studies were performed to estimate endogenous parathyroid secretion. As initial screening procedures, responses to the administration of parathyroid extract (Eli Lilly and Company) and calcium infusion were determined in K.B. and E.B. by measurement of %TRP before and after administration of these agents.

In addition, fasting blood was obtained from the two affected siblings and the older unaffected one for direct measurement of serum PTH levels. The sera obtained were assayed for PTH content by the immunoassay method of Berson et al.[19]

Vasopressin Administration

Urinary concentrating ability in patient K.B. was evaluated by overnight fasting (8 hr) followed by parenteral administration of 0.3 ml of aquesous vasopressin. Osmolalities were obtained on spontaneously voided urine collected during water deprivation and following vasopressin administration.

The response to vasopressin was also evaluated in patient E.B. He received intravenous vasopressin as has been previously described.[20] Following an oral water load of 20 ml/kg of body weight, aqueous vasopressin was infused at a concentration of 2.5 U/liter. The infusion was begun at 1 ml/min and the rate later doubled. Hourly blood and urine specimens were examined for sodium and osmolality. The urine excreted was replaced by an equal volume of oral water.

Magnesium Administration

Since the initial balance data obtained from K.B. and E.B. suggested excessive urinary magnesium losses, patient K.B. was further evaluated. A regimen was instituted during which the patient received oral magnesium supplement at a dosage of 120 meq/day for 7 days. During a subsequent study, the patient received intramuscular magnesium sulfate at a dosage of 20 meq/day for a similar period of time. During both of these periods serum, RBC, and urine magnesium determinations were made.

Blood and urine pH were measured with a pH meter (Radiometer, Copenhagen). Total carbon dioxide content (tCO_2) was measured with a Natelson microgasometer. Serum sodium and potassium were measured by flame photometry, chlorides on a Buckler chloridometer (Buckler Instruments, Inc., Fort Lee, N. J.), and osmolalities on an Advanced osmometer (Advanced Instruments, Inc., Newton Highlands, Mass.). Creatinine was measured by the method of Bonsnes and Taussky.[21] Calcium and magnesium were measured on an atomic absorption spectrophotometer. Phosphorus was also determined by spectrophotometric method. Urinary glucose was evaluated by the glucose oxidase method while urinary amino acids were determined by thin-layer chromatography.

RESULTS

Family Evaluation

Studies on the parent and five siblings revealed that only K.B., age 10, and E.B., age 6, demonstrated abnormalities (see Case Reports and Table 1). Both had serum bicarbonates below normal and both had x-ray evidence of bilateral nephrocalcinosis. K.B. also demonstrated decreased serum calcium and phosphorus, elevated alkaline phosphatase, and skeletal changes while no such abnormalities were noted in E.B. The other siblings and the mother all had normal blood, urine, and x-ray studies.

Acid Loading

Responses to ammonium chloride loading in the six family members are depicted in Table 2. All evidenced decreases in serum bicarbonate following administration of the agent, with the lowest levels being attained by K.B. and E.B. The three unaffected siblings and the mother demonstrated adequate urinary acidification, all decreasing urine pH below 5.0. In contrast, the lowest urine pH values obtained in K.B. and E.B. were 5.5 and 5.4, respectively, indicating an inadequate distal tubular hydrogen ion secretory capacity, especially in view of the marked decreases in serum bicarbonate.

Control Observations

With the siblings on ad lib. fluids and known diets, data were obtained from daily measurements of serum and 24-hr-urine collections as shown in Table 3.

The relatively high 24-hr-urine volumes noted in K.B. and E.B., in comparison to that observed in the older and larger sibling D.B., are consistent with their history of polyuria. Daily calcium excretion in patients K.B. and E.B. (151 and 133 mg, respectively) were excessive especially in view of the fact that patient K.B. was persistently hypocalcemic (mean serum level 6.2 mg/100 ml) and patient E.B. was ingesting 500 mg/day of calcium, a level below that recommended for his age (800 mg/day). D.B., also on a calcium-deficient intake, effectively decreased her urinary calcium losses to 32 mg/24 hr. The hypercalcuria noted in K.B. and E.B. was considered to be an expected accompaniment to their renal tubular acidifying defects.

Daily urinary magnesium losses were quantitated and compared with serum and erythrocyte levels. Serum (normal is 1.5–2.5 meq/liter) and erythrocyte (normal is 4.2–6.0 meq/liter) levels were decreased in K.B. and E.B., and both had relatively large urinary losses of magnesium. The losses of magnesium were greater than 5 meq/day in both patients while their serum levels were 1.2 meq/liter (K.B.) and 1.1 meq/liter (E.B.). Since urinary loss of magnesium can be reduced to 1 meq/day when conservation is induced,[22] the losses were felt to be excessive in view of their reduced serum levels. The response to magnsium loading in patient K.B. is described later in this section.

Finally, calculation of per cent tubular reabsorption of phosphate demonstrated normal values in E.B. and D.B., while the level in K.B. was 72.0%.

Table 2. Response to Acid (NH_4Cl) Load

Patient	Age (yr)	Wt (kg)	Body Surface (sq m)	NH_4Cl Dose (meq)	Serum HCO_3 (mmole/liter)*	Urine pH*
K.B.	10	25	0.93	140	10.0	5.5
E.B.	6	16	0.68	100	13.8	5.4
D.B.	13	44	1.36	200	14.7	4.8
C.B.	11	33	1.12	165	18.0	4.8
R.B.	8	25	0.90	135	14.1	4.8
J.B.	33	60	1.49	210	14.1	4.8

* Lowest value measured following NH_4Cl administration.

Calcium Absorption Studies

Studies of patient K.B. on two separate occasions demonstrated decreased gastrointestinal absorption of ^{47}Ca. Following oral administration of the agent, plasma levels demonstrated peak activities of less than 1% of the administered dose per liter of plasma. In E.B., however, a normal absorption curve was obtained with normal appearance of radiocalcium in the serum, a level of greater than 3% of the administered dose appearing in 45 min. Further, in E.B., but not K.B., 4-hr urinary excretion of the agent was approximately 0.7% of the dose, an amount considered normal as reported by Avioli et at.[17]

Bicarbonate Infusion

The observations made during bicarbonate infusion in the two affected siblings (K.B. and E.B.) and the normal sister (D.B.) are summarized in Table 4. The levels of bicarbonate threshold were depressed in K.B. and E.B. while a normal value of 26 mmole/liter was obtained in D.B. The differences in the threshold in the affected siblings are consistent with the observation that control serum bicarbonate levels in patient E.B. were only mildly depressed while levels in patient K.B. were consistently found to be below 21 mmole/liter.

The observation of the decreased bicarbonate threshold would initially suggest an isolated defect in proximal bicarbonate reabsorption as has previously been described.[4] However, such patients should then adequately acidify the urine when serum bicarbonate levels below threshold are attained. The failure of both siblings to achieve adequate urinary acidification at markedly reduced serum bicarbonate levels during acid loading, suggests that the distal tubular acidifying mechanism was also defective in these patients.

Table 3. Summary of Control Observations*

	K.B. (0.93/sq m)	E.B. (0.68/sq m)	D.B. (1.36/sq m)
Daily fluid Volume ingested (cc)	3,350	1,800	1,800
Serum			
Calcium (mg/100 ml)	6.2	9.2	9.1
Phosphorus (mg/100 ml)	4.1	4.8	5.1
Magnesium (meq/liter)			
Serum	1.2	1.1	1.8
RBC	3.6	3.7	4.8
Creatinine (mg/100 ml)	1.1	0.8	0.8
Urine			
Daily urine Volume excreted (cc)	3,100	1,700	1,500
Daily calcium excretion (mg)	151	133	32
Daily magnesium excretion (meq)	6.0	5.3	7.4
Tubular reabsorption of phosphate (%)	72.0	86.3	90.8

* Mean of 10-days' observation.

Table 4. Serum Bicarbonate Threshold with Simultaneous pCO_2 and Electrolytes*

Patient	Bicarbonate Threshold (mmole/liter)	pCO_2 (mm Hg) C	Th	Na (meq/liter) C	Th	K (meq/liter) C	Th	Cl (meq/liter) C	Th
K.B.	18.8	27	35	131	131	3.8	3.6	109	109
E.B.	21.3	30	31	131	135	3.4	3.2	100	96
D.B.	26.0	31	37	137	138	4.3	3.8	99	109

* C is the value during the control period; Th is the value at threshold.

Evaluation of Endogenous PTH Secretion

In patient K.B., control %TRP was 72.3% and decreased to only 67.1% as calculated from a 24-hr urine on the third day of PTE administration. Such a response might result either from already elevated endogenous PTH levels (the control %TRP was low) or from a fixed abnormality of the proximal renal tubules. Response to calcium infusion, however, seemed to contradict the latter hypothesis since control measurement of %TRP on a 2-hr morning urine collection was 61.4% prior to calcium administration and increased to 76.2% following overnight calcium infusion. In patient E.B. similar studies demonstrated entirely normal responses.

Direct measurement of serum PTH levels by immunoassay suggested that patient K.B. had an elevated level (1.4 ng/ml of serum) while those of E.B. and the unaffected sibling (<0.4 ng/ml) appeared normal (Table 5). These findings seemed to correlate well with the indirect studies performed to assess levels of PTH secretion.

Vasopressin Administration

The maximal urine osmolality observed in patient K.B. following fluid deprivation and vasopressin administration was 248 mOsm/kg H_2O while that observed in E.B. was 275 mOsm/kg H_2O. Both values were less than simultaneous plasma levels. The failure to produce a concentrated urine in response to vasopressin administration in K.B. and E.B. is consistent with the history of polyuria and the finding of nephrocalcinosis in both patients.

Magnesium Administration

During hospitalization patient K.B. was given oral and intramuscular magnesium supplements in an attempt to correct her decreased serum magne-

Table 5. Serum Parathyroid Hormone Assay*

K.B.	1.46 ng/ml
E.B.	<0.4 ng/ml
D.B.	<0.4 ng/ml

* Normal levels considered up to 0.8 ng/ml.

sium levels. The serum and red-blood-cell levels and urinary response are depicted in Table 6. Oral magnesium (120 meq/day) for 7 days produced essentially no change, except for transient increases, in serum and red-blood-cell magnesium levels. One week later a course of i.m. magnesium at a dose of 20 meq/day was given and again little response was obtained. This is in contrast to previous experience with hypomagnesemia[23,24] in which prompt restoration of serum levels follows parenteral administration. The lack of response can be explained by the rise in urinary excretion of magnesium from control values of 6.0 meq/24 hr to mean levels of 11.8 and 12.7 meq/24 hr, respectively, during oral and intramuscular loading.

K.B. was placed on oral magnesium supplement for 4 wk following discharge from the hospital again with no change in serum magnesium levels (biweekly determinations). The development of diarrhea in the fifth wk of therapy resulted in its discontinuance.

DISCUSSION

Two siblings with nephrocalcinosis and decreased distal tubular hydrogen ion secretory capacity were found to have a decrease in the renal bicarbonate threshold and decreased serum and erythrocyte magnesium levels. Significant bicarbonate wasting is not considered part of the syndrome of classical (that is, distal) RTA[25,26] although mixed defects have been described.[1] Hypomagnesemia has been previously noted in a variety of chronic renal diseases[27] including RTA,[28] although precise etiology remains uncertain.

The effects of increased PTH secretion on the renal tubule have been invoked to explain proximal tubular dysfunctions such as phosphaturia and amino aciduria observed in vitamin D-resistant rickets[29] and in vitamin D

Table 6. Response of K. B. to Oral and Parenteral (i.m.) Magnesium Administration

	Magnesium Determinations			
	Serum meq/liter	RBC meq/liter	Urine meq/day	Urine mg/kg body weight/day
Control	1.2	3.6	6.0	2.9
Oral supplement (120 meq/day)				
Day 1	1.2	4.0	9.5	4.6
3	1.4	4.4	12.0	5.8
5	1.4	4.2	12.7	6.1
7	1.3	4.0	13.0	6.2
I.M. supplement (20 meq/day)				
Day 1	1.4	3.8	12.1	5.8
3	1.5	3.9	14.2	6.8
5	1.2	4.1	12.0	5.8
7	1.0	4.1	12.5	6.0
Values 2 wk postdischarge	1.2	3.9	—	—

deficiency.[30,31] Such formulations have been supported by experimental observations demonstrating a decrease in amino aciduria and phosphaturia following parathyroidectomy in animals made deficient in calcium and/or vitamin D.[32] Further, the recent observation that parathyroidectomy can result in normalization of renal phosphate handling in adult-onset vitamin D-resistant rickets[29] supports such interpretations.

That increases in PTH levels might result in abnormalities of proximal tubular bicarbonate handling as well seems a reasonable formulation. The early studies of Ellsworth and Howard[33] demonstrated an increase in urine pH to follow parathyroid hormone infusion, and more recent studies have shown that bicarbonaturia does, in fact, occur following intravenous PTH.[7] The bicarbonaturia, furthermore, precedes the development of phosphaturia suggesting that it does not result from increased phosphate buffering of hydrogen ion in the tubular fluid. In addition, patients with nonrenal disorders considered likely to result in increased PTH secretion have been shown to evidence renal bicarbonate wasting.[8]

The distal tubular acidification defect demonstrated in the two affected children can be attributed to a primary decrease in the ability of the distal nephron to secrete the hydrogen ion.[26,34] That the affected siblings, K.B. and E.B., were able to reduce the pH of their urines to 5.5 and 5.4, respectively, is consistent with prior observations[9,35,36] that the syndrome of distal renal tubular acidosis may occur in other than the commonly described forms in which urinary pH is not seen to go below 6.0. The lack of a constant loss of bicarbonate at all levels of serum bicarbonate, which would be expected in classical (distal) RTA, is explained by the fact that the urine pH levels attained during acid loading were sufficiently low (below 6.0) to rid the urine of all bicarbonate.

The course of the disease observed in the two siblings may be in keeping with prior observations that patients may present with nephrocalcinosis (which may or may not precede the development of hypercalciuria) and normal serum electrolytes, and, when followed, be noted in time to develop the complete syndrome of classical renal tubular acidosis.[37] When electrolytes are normal, the disorder nevertheless exhibits a defect in urinary acidification which can be demonstrated by ammonium chloride administration, and such patients have been described as having "incomplete renal tubular acidosis," a term originally suggested by Wrong and Davies.[9] Such observations suggest that patients with unexplained hypercalciuria or nephrocalcinosis should be studied with an acid load so that if defects in urinary acidification are demonstrated the patients can be closely followed and appropriately treated if the complete form of the disease develops.

The minimal bicarbonaturia which has been observed in distal or classic RTA has been carefully studied and is thought to be secondary to decreased distal hydrogen ion secretion.[26,38] Mixed abnormalities, such as those described by Morris,[1] and the findings in our patients of decreases in the distal tubular urinary acidifying ability associated with depression of proximal tubular bicarbonate threshold seem less easily characterized. The possible role of

parathyroid hormone in the development of the abnormalities of the bicarbonate threshold observed, was therefore evaluated by studies to determine the level of parathyroid hormone secretion in each of the two patients.

That the endogenous secretion of parathyroid hormone was elevated in patient K.B. was suggested by the initial laboratory data which demonstrated a low serum calcium (6.0 mg/100 ml), low serum phosphate (3.5 mg/100 ml), elevated serum alkaline phosphatase, and the x-ray finding of an absent lamina dura. Gastrointestinal absorption of ^{47}Ca appeared impaired and it was theorized that decreased absorption of calcium in association with the observed hypercalciuria, would be expected to aggravate or, perhaps, have caused the decreased serum calcium levels, to which the parathyroid glands responded by increased secretion of parathyroid hormone.

The finding in patient K.B. (mean of 10-days' observation) of a decreased percent tubular reabsorption of phosphate (72.0%), a blunted decrease of %TRP following parenteral parathyroid extract administration (73.3%-67.1%), and the increase in %TRP following calcium infusion (61.4%-76.2%) all tended to confirm the suspicion of high endogenous secretion of parathyroid hormone. The response to calcium infusion also demonstrated that the parathyroids were not functioning autonomously and that the renal tubular handling of phosphate was dependent on extrarenal stimuli. As described above, immunoassay of the patient's serum also demonstrated a level of circulating parathyroid hormone of 1.46 ng/ml of serum, a value greater than the upper limit of normal (0.8 ng/ml).

Studies in the other affected sibling (E.B.) suggested no abormalities of PTH secretion. Initial serum determinations, %TRP, responses to parenteral parathyroid extract, and calcium infusion studies all were normal. Finally, immunoassay of serum from E.B. and a normal sibling D.B. for parathyroid hormone demonstrated normal levels. It might be speculated that normal gastrointestinal calcium absorption, as suggested by the normal ^{47}Ca absorption study observed in E.B., spared him from developing the increased level of PTH secretion observed in K.B.

Comparison of the data from the two affected siblings suggests, therefore, that abnormalities in the renal bicarbonate threshold as observed in these patients may accompany distal tubular acidifying defects and result from a defective proximal tubular mechanism for bicarbonate reabsorption unrelated to the presence or absence of excessive PTH. The bicarbonate abnormality when present, however, would be expected to dictate increased requirements for bicarbonate therapy.

It is further indicated that neither vitamin D resistance nor secondary hyperparathyroidism is necessary for the development of nephrocalcinosis in these disorders. The vasopressin-resistant defect in renal concentrating ability observed in both patients, however, can be attributed to disruption of the renal medulla secondary to nephrocalcinosis as previously suggested.[26,39] The additive effect of recurrent urinary infection must also be considered in K.B.

The two affected siblings studied were also found to be hypomagnesemic.

Since primary hyperparathyroidism is well recognized as a cause of hypomagnesemia,[15,16,40] and since parathyroid extract, when administered for prolonged periods, has been demonstrated to result in increased urinary magnesium losses,[13,14] studies of magnesium handling were performed and the role of parathyroid hormone in relation to the observed abnormalities was assessed.

With the daily intake of magnesium at 200–250 mg per day as calculated by the diet kitchen, and with decreased serum magnesium levels of 1.2 and 1.1 meq/liter, respectively, for K.B. and E.B., both patients were observed to excrete excessive amounts of magnesium into their urine. Since it was considered that the increased urinary magnesium levels indicated a failure of renal conservation, patient K.B. was given oral and later intramuscular magnesium loads in an attempt to further characterize this abnormality.

She responded to both regimens in a similar manner. There was a twofold increase in the daily urinary excretion of magnesium during both oral and intramuscular loading. The increase with oral administration suggested adequate gastrointestinal absorption. The serum values, however, were unchanged following the treatment periods. The data, therefore, suggest that the hypomagnesemia noted in these patients is at least in part the result of excessive renal loss of magnesium. Since endogenous parahyroid hormone secretion appeared elevated in patient K.B., but not in patient E.B., one may conclude that increased PTH secretion was not responsible for the observed urinary magnesium losses. Previous experimental data have suggested that the hypermagnesuria demonstrated in both patients may be related to the hypercalciuria also observed.[41]

The responsiveness to endogenous and exogenous PTH noted in our patients indicated that the serum magnesium levels observed were not sufficiently lowered to interfere with PTH effect, as has been reported in connection with PTH-unresponsive hypocalcemia secondary to hypomagnesemia.[42] It seems worthy of consideration, however, that in other patients with RTA, magnesium levels may decrease to a degree that hypocalcemia either develops or is made worse as a result of magnesium depletion. In such instances, magnesium administration may provide a useful aid to the standard therapy of hypocalcemia when seen in these patients.

ADDENDUM

Following discharge, patient K.B. was continued on the alkali and vitamin D (calciferol 200,000 U/day) therapy begun during hospitalization. Only slight improvement in serum calcium was noted in 3 mo of outpatient follow-up (mean serum calcium 7.2 mg/100 ml). However, in the fourth month, a rise of serum calcium did occur (8.7 mg/100 ml) permitting a decrease in calciferol dosage to 100,000 U/day, suggesting a therapeutic response despite some degree of continued vitamin D resistance. E.B., the younger sibling, has been placed on alkali therapy alone. Serum bicarbonate levels in both patients have been maintained at normal levels. Their hypomagnesemia has persisted.

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