PROBLEMS IN THE DIFFERENTIATION OF THE MILK-ALKALI (BURNETT'S) SYNDROME AND HYPERPARATHYROIDISM, ILLUSTRATED BY TWO CASE REPORTS

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THE milk-alkali (Burnett's) syndrome and hyperparathyroidism under certain circumstances may be practically indistinguishable clinically.[1] Those special circumstances are illustrated in the two case histories that will be presented following a brief comparison of the characteristics, causes, and courses of the two diseases.

Burnett's syndrome is characterized by hypercalcemia without hypercalciuria (Table). It does not cause skeletal damage. The etiologic factor is the excessive intake of milk and absorbable alkali. The condition eventually results in renal failure, but just before renal failure, hypocalciuria becomes evident in an alkaline urine.

TABLE

Anticipated Findings in Milk-Alkali (Burnett's) Syndrome and in Hyperparathyroidism with Associated Renal Insufficiency

Factors	Milk-Alkali (Burnett's) Syndrome	Hyperparathyroidism with Associated Renal Insufficiency
Serum calcium	Increased	Increased
Serum phosphorus	Normal	Normal or increased
CO_2-combining power	Elevated or normal	Normal or low
Urinary pH	High (above 7.0)	Low (below 7.0)
Urinary calcium excretion	Low	High (late in course of disease it may be low)
Cystic bone disease	Absent	Absent in more than 50% of cases
History of intake of milk and absorbable alkali	Present	Absent

Hyperparathyroidism is characterized by hypercalcemia with high urinary calcium excretion, which eventually results in renal failure. However, when renal failure occurs as a late complication of the disease, the low serum phosphorus and the hypercalciuria may disappear, and as in Burnett's syndrome, hypercalcemia without hypercalciuria exists (Table). In about one third of the patients having hyperparathyroidism there is skeletal damage, and pathognomonic roentgenographic findings are osteitis fibrosa cystica and absence of the dental lamina dura. The etiologic factor generally is a tumor of one or more parathyroid glands, which when aberrant may be situated somewhere in the mediastinum.

CASE REPORTS

Case 1. A 63-year-old farmer was first seen on April 26, 1954. His presenting complaint was that of daily "heartburn" of many years' duration. His appetite had become poor and he had lost 5 pounds in weight during the previous month. He had muscular weakness, constipation, moderate thirst, and nocturia.

Findings on physical examination were not unusual. However, a KUB roentgenogram disclosed a semicircular opaque shadow within the left renal pelvis. The blood-urea content was 150 mg./100 ml. The blood-urea clearance rate was 14 per cent at the end of the first hour and 12 per cent at the end of the second hour. The red blood cell count was 3,380,000/cu. mm. and the hemoglobin content was 9.2 Gm./100 ml. The initial serum calcium was 15.9 mg./100 ml. and the initial serum phosphorus 4.0 mg./100 ml. Subsequent determinations of serum calcium were 16.0, 14.9 and 15.2 mg./100 ml., and of serum phosphorus 4.0, 3.2 and 1.6 mg./100 ml. The total serum protein content was 7.4 Gm./100 ml. with an albumin of 4.5 Gm. and a globulin of 2.9 Gm./100 ml. The urine had a specific gravity of 1.012 with a pH of 7.5. A urinary calcium excretion on the third day of a fixed calcium intake of 140 mg./24 hours, was 450 mg./24 hours (the upper normal value in our laboratory on this diet is 150 mg./24 hours).

Because of the hypercalcemia with hypercalciuria, hyperparathyroidism was considered the most likely diagnosis and the most likely cause of the renal insufficiency. On careful questioning, the patient admitted the consumption of milk but denied the use of absorbable alkali. The serum phosphorus level was relatively low—lower than ordinarily would be expected in a patient with this degree of renal insufficiency, particularly the one determination of 1.6 mg./100 ml. The finding of this low value for serum phosphorus is not explicable, particularly since subsequently a similarly low value was obtained. However, the skeletal damage that frequently is found in hyperparathyroidism was absent; skeletal roentgenographic findings were normal; and the dental lamina dura was present. An intravenous calcium-load test, according to the technic of Howard,[2] was performed. The control excretion of phosphorus was 80 mg./24 hours on the third day of a low-phosphorus diet. On the fourth day 30 mg. of calcium gluconate per kilogram of body weight was given in saline over a four-hour period. During the infusion of calcium the hourly serum phosphorus determinations were as follows: Fasting, 2.2 mg.; one hour, 2.0 mg.; two hours, 2.1 mg.; three hours, 1.9 mg.; and four hours, 2.4 mg./100 ml. The total urinary phosphorus excretion on that day was 60 mg. The test was evaluated as follows: A normal test is accompanied by a rise in serum phosphorus and a fall in urinary phosphorus. Patients with parathyroid tumor show a fall in serum phosphorus and a rise

in urinary phosphorus. In this patient there was a fall in serum phosphorus but no rise in urinary phosphorus.

On May 12, 1954 (16 days after the initial visit), the neck was explored for a parathyroid tumor. No parathyroid tumor or hyperplasia was found. Hypercalcemia persisted and on October 14, 1954, the mediastinum was thoroughly searched for a parathyroid tumor but none was found. It was then learned that the patient had carefully concealed the fact that with the daily consumption of a large amount of milk he also had for several years eaten "Tums" in large quantities in an attempt to control the "heartburn." This practice was immediately discontinued, and on October 18, 1954, the serum calcium was 11 mg. and the serum phosphorus 4 mg./100 ml., with a total serum protein of 7.1 Gm./100 ml. The serum calcium on June 9, 1955, was 9.9 mg. with a serum phosphorus of 3.3 mg./100 ml. and a blood urea of 24 mg./100 ml. The blood-urea clearance rate had increased to 47 per cent the first hour and 41 per cent the second hour (formerly, 14 and 12 per cent respectively).

Comment: This patient now is regarded as having had Burnett's syndrome and not hyperparathyroidism. The excessive intake of milk and absorbable alkali for a period of years, and the hypercalcemia so induced led to renal insufficiency but not to hypocalciuria as is usually present in Burnett's syndrome. The urinary pH value of 7.5 persisted until the patient discontinued taking absorbable alkali, whereupon the urinary pH fell to 6.8. The prompt disappearance of the hypercalcemia and the fall both in blood urea and in urinary pH with the discontinuance of milk and alkali favor this diagnosis, which is further supported by the negative surgical exploration of the neck and of the mediastinum for parathyroid tumor.

The normal skeletal findings can be explained on the basis of an excessive intake of milk that presumably protects the skeleton from decalcification, but the important consideration from a clinical point of view is that the absence of bone disease tends to indicate the presence of Burnett's syndrome. It is of course clearly recognized, as mentioned earlier, that only about one third of the patients with hyperparathyroidism have skeletal damage, so that its absence in this case did not exclude hyperparathyroidism as a cause of hypercalcemia. Patients with hyperparathyroidism and renal insufficiency from nephrocalcinosis will have hypercalcemia without a low serum phosphorus and eventually will lose their hypercalciuria (illustrated in Case 2). This combination is far more common than is hyperparathyroidism with skeletal damage either with or without renal disease.

Case 2. A 26-year-old office worker was first seen on February 15, 1955. His presenting complaint was that of aching discomfort in his heels, and weakness in the knees of four years' duration. He stated that on bending forward his knees felt stiff and that they were painful on the anterior surfaces. His thirst was extreme and he had nocturia four to six times each night. He stated that he consumed large quantities of milk, from 2 to 5 quarts daily, and that he had done this for a number of years. There was no history of excessive consumption of vitamin D or alkali. There was no past history of renal disease.

Physical examination disclosed extreme reflex excitability of all tendon reflexes, yet muscular tone was flabby. Despite his muscular wasting he was able to walk five to eight miles each day. His hand grip was above normal. There was clubbing of the fingers, a rare occurrence in hyperparathyroidism. Lateral nystagmus was present. Roentgenographic examination revealed cystic changes in the long bones, diffuse mottling of the

skull with a "ground-glass" appearance, and absorption of the dental lamina dura. The total serum calcium was 13.8 mg. and serum phosphorus was 7.2 mg./100 ml. Alkaline phosphatase measured 11.2 Bodansky units. Recheck serum calcium and serum phosphorus were 12.0 mg. and 7.3 mg./100 ml., respectively, and alkaline phosphatase measured 11.7 Bodansky units. Numerous subsequent determinations for serum calcium and serum phosphorus disclosed levels comparable to those mentioned; serum phosphorus levels were as high as 8.3 mg./100 ml. The total serum protein was 9 Gm./100 ml., with an albumin of 4.6 Gm. and a globulin of 4.4 Gm./100 ml. A recheck total serum protein measured 7.9 Gm. with an albumin of 3.8 Gm. and a globulin of 4.1 Gm./100 ml. The plasma creatinine was 6.4 mg./100 ml., and the blood urea 189 mg./100 ml. The CO_2-combining power was 21.2 volumes per cent, and plasma chlorides were 544 mg./100 ml. Hemoglobin content was 12.0 Gm./100 ml., with a red blood cell count of 4,630,000/cu. mm., and a total cell volume of 40 ml./Kg. of body weight. The blood-urea clearance rate was 14 per cent at the end of the first hour and 13 per cent at the end of the second hour. On a 12-hour night urine collection, the urine had a specific gravity of 1.008, with a pH of 6.0 and a protein excretion of 0.9 Gm. Urinary calcium excretion on the third day of a controlled calcium diet was 67 mg./24 hours (upper normal 150 mg./24 hours).

The diagnosis of primary hyperparathyroidism was considered because of the hypercalcemia, the cystic bone disease with absence of dental lamina dura, the elevated alkaline phosphatase and the renal failure. The renal failure was considered to be secondary to the hypercalcemia and was regarded as resulting from nephrocalcinosis. There were no hypertension, significant anemia, or proteinuria, which made it seem unlikely that primary renal disease was the problem. Furthermore, patients with secondary hyperparathyroidism usually are found not to have bone disease with this degree of severity nor do they present hypercalcemia. The diagnosis of Burnett's syndrome was considered, but it was excluded by the presence of bone disease with destruction of dental lamina dura, osteitis fibrosa cystica, and a high alkaline phosphatase. Bone disease does not occur in typical Burnett's syndrome. Furthermore, there was no history of excessive consumption of alkali, and it is necessary that absorbable alkali be consumed with excessive amounts of milk in order to cause hypercalcemia. The urinary pH of 6.0 and the low CO_2-combining power also were incompatible with Burnett's syndrome.

The absence of hypercalciuria and the presence of an elevated serum phosphorus were believed to be due to renal failure induced by the hypercalcemia of primary hyperparathyroidism. During an intravenous calcium-load test, performed as in Case 1, the serum phosphorus fell from a level of 7.0 mg. to a level of 6.2 mg./100 ml., and the urinary phosphorus rose from a control excretion level of 70 mg. to a level of 93 mg./24 hours. Because of this and other findings indicating the diagnosis of primary hyperparathyroidism, an exploratory operation was performed on May 13, 1955, three months after the initial visit. A parathyroid adenoma, chief cell in type, was found on the left upper parathyroid; it measured 3 by 1.5 by 1 cm. Following the removal of the parathyroid tumor the serum calcium level fell to 7.0 mg./100 ml., resulting in active tetany that required administration of calcium and vitamin D. Blood urea fell to 57 mg./100 ml. on the fourth postoperative day. A few days later the patient was discharged and was advised to continue taking vitamin D, 50,000 units four times daily, and calcium lactate, 6 drams per day. This therapy allowed the blood calcium to reach levels of approximately 8.5 to 9 mg./100 ml. in four weeks.

Discussion

It is believed that the two cases clearly present many of the problems inherent in differentiating between milk-alkali syndrome and hyperparathyroidism. The first patient, who had consumed milk and alkali for a number of years, had renal failure, hypercalcemia, an alkaline urine, and, despite renal failure, hypercalciuria. The last is an extraordinary occurrence in Burnett's syndrome. Bone disease was absent, as it might be in either Burnett's syndrome or primary hyperparathyroidism. The prompt disappearance of azotemia and the fall to normal of the serum calcium level upon the discontinuance of absorbable alkali was followed by a partial recovery and an improvement of renal function. The second patient, with primary hyperparathyroidism, had renal failure of a degree sufficient to lower the urinary calcium excretion, on a controlled diet, to 67 mg./24 hours. This is the lowest 24-hour urinary excretion of calcium in any case of hyperparathyroidism that has been recorded in the literature. The urine was always acid in reaction. The bone lesions, with cystic changes in the skull and disappearance of the dental lamina dura, were of a degree incompatible with Burnett's syndrome or with secondary hyperparathyroidism. The absence of anemia, of proteinuria, and of hypertension was incompatible with a diagnosis of primary renal failure with secondary hyperparathyroidism.

Hypercalcemia regardless of its cause is accompanied by polyuria, nocturia, muscular weakness, and anorexia. The renal insufficiency seen in Burnett's syndrome is in no way different from that seen in other disorders in which hypercalcemia has led to nephrocalcinosis. Patients with "nephrocalcinotic renal failure" usually do not appear to be ill. The elevated urinary pH in the presence of hypercalcemia is a point in favor of the diagnosis of Burnett's syndrome when there is no history of excessive intake of milk and absorbable alkali.

It has been suggested that Burnett's syndrome might be an atypical hyperparathyroidism. This suggestion appears to be untenable for several reasons: Hypercalcemia and with it renal failure, hypocalciuria, and high urinary pH, develop in only a few patients who ingest milk and alkali for treatment of duodenal ulcer or hyperacidity. Furthermore, discontinuance of the milk and alkali leads to a prompt fall in the urinary pH, increased urinary excretion of calcium, a fall in serum calcium and, within a few days, reduction in blood urea. Such quick changes would not be expected in hyperparathyroidism, either primary or secondary in type. A negative parathyroid and mediastinal exploration (as in Case 1) further supports the nonparathyroid source of the hypercalcemia in Burnett's syndrome.

Summary

Findings in two cases, one of milk-alkali (Burnett's) syndrome and the other of primary hyperparathyroidism, are reported to illustrate the occasional difficulties in differentiating these conditions. The presence of hypercalciuria in the patient having Burnett's syndrome and its absence in the patient having hyper-

parathyroidism are rare occurrences. In the latter patient, the phenomenon apparently was a manifestation of a severe degree of renal failure.

The responses to an intravenous calcium-load test were of diagnostic value in both patients, showing no change in serum phosphorus and lowered urinary phosphorus in the patient having Burnett's syndrome; and a lowered serum phosphorus and an elevated urinary phosphorus in the patient having hyperparathyroidism. The response was not compatible with a diagnosis of hyperparathyroidism in the patient with Burnett's syndrome; but in the patient having primary hyperparathyroidism, the response was compatible with the latter diagnosis.

References

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