DIAGNOSIS OF OBSCURE HYPERPARATHYROIDISM

ROBERT W. SCHNEIDER, M.D.
Department of Endocrinology
and
A. H. ROBNETT, M.D.
Department of General Surgery

MUCH has been written concerning the overt clinical features of hyperparathyroidism and, when the condition leads to osteitis fibrosa cystica and renal calculi, it is easily recognized. It is not the purpose of this article to re-emphasize the classical clinical findings in cases of this type, but to call attention to some of the more unusual manifestations of the condition and to present some practical considerations which may be of value in the recognition of the less typical hyperparathyroidism.

The classical blood chemical alterations of hyperparathyroidism are hypophosphatemia and hypercalcemia, the latter due to elevation in the ionic calcium fraction of the serum. Two case reports presenting factors which obscure the existence of these alterations are presented.

Case Reports

Case 1. A college professor 32 years of age presented a history of recurrent right and left renal calculi for over a period of 1 year. The initial stone, removed from the left renal pelvis 1 month after onset of illness, was composed of calcium phosphate. Two small stones in the right renal pelvis were visualized by x-ray and at the time of initial operation were observed to have increased in size. In the left kidney a second large calculus appeared shortly after the nephrolithotomy; several others had been passed. Progressive fatigue had been apparent for a period of 2 years. Pain was experienced at times in the back, the shoulders, and knees. The fingernails had become "shabby." No polydipsia, polyuria or nocturia had been noted.

Studies by Dr. Charles A. Hulse in Tulsa, Oklahoma, the referring physician, disclosed serum calcium levels of 12.0, 13.0, 10.7, 12.0, and 11.6 mg. per cent. Serum phosphorus values were 2.2, 1.5, 2.4, 2.2, and 2.4 mg. per cent. Renal function was estimated as normal (method unknown). Total blood protein was 6.9 Gm. per cent. Twenty-four hour urine calcium excretion was 445 mg.

General physical examination was not pertinent. Our laboratory findings, 6 months after those of Dr. Hulse, showed serum calcium levels of 10.3, 12.4, and 11.1 mg. per cent. Serum phosphorus levels were measured at 2.5 mg. per cent on two occasions. Alkaline phosphatase was repeatedly normal ranging from 2.0 to 2.9 Bodansky units. Urea clearance test of kidney function was within normal limits. Total blood proteins measured 5.2 Gm. per cent. Urine Sulkowitch test was consistent with hypercalciuria, and x-rays of the teeth failed to show resorption of the lamina dura. Roentgenologic examination of the chest and barium esophagram were negative. Plain film of the abdomen disclosed bilateral renal calculi. When allowance was made for the low total protein, the serum calcium values in reality ranged between 12.0 and 14.0 mg. per cent.

On the basis of the laboratory findings and history of recurrent renal calculi, a diagnosis of hyperparathyroidism with bilateral renal calculi and without bone involvement was made. An adenoma, involving the left inferior parathyroid gland, 1 cm. in

diameter, was found lying deep in the tracheoesophageal groove. Microscopically the tumor consisted of chief cells, transitional cells and clear cells, all of which were well differentiated. There was no evidence of blood vessel invasion.

Postoperatively serum calcium determinations measured 9.1 and 9.0 mg. per cent at a time when his total serum protein was 6.8 Gm. per cent and phosphorus 2.2 and 2.7 mg. per cent. The patient has been in good health for a period longer than 2 years.

Case 2. On September 20, 1949 a white woman of 64 years was first admitted to the Cleveland Clinic Hospital with a typical severe duodenal ulcer syndrome of 4 months' duration. She had been known to have had diabetes mellitus for 8 years, but was well managed on a 1200 calorie diet and the administration of 20 units of protamine zinc insulin plus 15 units of regular insulin daily. She had been confined to bed for a year because of pronounced muscular weakness.

Observations on physical examination were within the expected (normal) limits compatible with her age except for bilateral nuclear cataracts, a small diffusely nodular goiter, and some stiffness in the left sacro-iliac joint.

Laboratory studies which included a complete blood count, urinalysis, serology and amylase determinations were within normal limits. However the serum calcium was 12.5 mg. per cent and serum phosphorus 3.3 mg. per cent, while the Sulkowitch test for urine calcium was normal. Urea clearance was significantly depressed. The gastric analysis, using an Ewald test meal, disclosed a free acid of 32 and a total acid of 48.

X-ray examination revealed a duodenal ulcer as well as moderate hypertrophic arthritis of the lumbar vertebra and right hip joint. The diagnosis of duodenal ulcer and diabetes mellitus was established and the patient placed upon appropriate therapy with immediate regression of her symptoms. She was discharged from the hospital on the sixteenth postoperative day.

During the ensuing 10 months abdominal pain was absent but there was a daily emesis of all or part of one or more meals. Three weeks prior to readmission to the Clinic Hospital (July 21, 1950), epigastric pain returned accompanied by an unremitting nausea with repeated daily vomiting.

Physical examination upon admission disclosed an acutely ill, lethargic hyporeflexic patient. Other findings corresponded to those observed at the time of previous hospitalization.

The admission laboratory studies revealed the urine to contain numerous white blood cells although culture was sterile. A mild microcytic hypochromic anemia was present. Other laboratory studies were: blood sugar 183 mg. per cent, blood urea 72 per cent, CO^2 combining power 54.1 volumes per cent, serum amylase 76 units, serum protein 6.0 Gm. with albumin globulin ratio 3.8/2.2. The serum calcium was 11 mg. per cent and serum phosphorus 4.3 mg. per cent. The Sulkowitch test was negative. Urea clearance was depressed to a value of 36 per cent of normal.

Roentgenologic examination of the gastrointestinal tract again disclosed a duodenal ulcer and a regimen of ulcer management was instituted. The patient, however, remained lethargic, hyporeflexic, and did not respond clinically to intensive ulcer therapy.

Repeated determinations of the serum calcium ranged from 10.4 to 11.5 mg. per cent while serum phosphorus varied from 1.3 to 3.3 mg. per cent. The Sulkowitch test for urinary calcium was intermittently positive. Accordingly a diagnosis of parathyroid adenoma was considered. On August 8, 1950 the neck was explored and a parathyroid adenoma 2 by 1.2 by 0.8 cm. in diameter weighing 0.5 Gm. was found in the lower pole of the left lobe of the thyroid. Further exploration revealed the presence of a nodular goiter but no other parathyroid tumor. Accordingly the left lobe of the thyroid was resected including the parathyroid adenoma. The right lobe, although nodular, was not resected.

The postoperative convalescence was uneventful and vomiting ceased immediately. On the third postoperative day the blood calcium was 9.6 mg. per cent and the phosphorus 2.6 mg. per cent. Normal biceps and triceps reflexes were obtained for the first time since admission. Therapy consisted of antacids, simple diet, and diabetic management with subsequent rapid improvement of the patient and regression of all symptoms.

The patient returned for examination 2 months later and was found to be asymptomatic. The serum calcium was 11.0, phosphorus 4.1, urea 75; urea clearance was 25 per cent of normal. X-ray study of the upper gastrointestinal tract disclosed a healing duodenal ulcer and the patient remained on a modified ulcer regimen.

Four months postoperatively gastrointestinal x-rays failed to demonstrate an ulcer crater for the first time and the patient was symptom free. Serum calcium, phosphorus and total proteins were normal: 10.0 mg. per cent, 4.8 mg. per cent, and 7.6 Gm. per cent. Urea clearance was 66 per cent of normal.

Discussion

The diagnosis of hyperparathyroidism depends upon a satisfactory concept of basic parathyroid physiology; an awareness that there is no single diagnostic pattern of signs and symptoms; a suspicion of the condition in the presence of suggestive signs and symptoms, and laboratory confirmation of the suspicion. Essentially in hyperparathyroidism, the overproduction of parathyroid hormone causes *hyper*phosphaturia and *hypo*phosphatemia followed by hypercalcemia and eventual hypercalciuria. In hypoparathyroidism the reverse occurs, with *hypo*phosphaturia and *hyper*phosphatemia followed by *hypo*calciuria and *hypo*calcemia.

The exact mode of action of parathyroid hormone on the calcium-phosphorus mechanism has not been determined fully. Albright[1] considers that parathyroid hormone renders body fluid phosphates more readily excretable by the kidney and believes that the changes in calcium metabolism are a secondary phenomenon. Ellsworth[2] believes the hormone lowers the renal phosphate threshold. Selye[3] postulates a primary action in bones while Harrison and Harrison[4] conclude that the hormone depresses renal phosphate reabsorption. Fay et al[5] have noted no direct effect upon the kidney. Jahan and Pitts[6] have recently reinvestigated the problem and their observations lend support to Albright's hypothesis.

While emphasis has been placed upon alterations in calcium metabolism in parathyroid disease, far too little attention has been given the value of the serum phosphorus levels. In many disease states there are high serum calcium levels, high urinary calcium excretion, and high urinary phosphate excretion. In striking contrast and with rare exception, low serum phosphorus levels are the sine qua non of hyperparathyroidism.

Recurrent renal calculi or cystic bone changes most commonly indicate the diagnosis of hyperparathyroidism, but these manifestations are often absent. Furthermore, preoperative demonstration of a parathyroid adenoma is an infrequent occurrence. Norris[7] found that only 10 per cent of parathyroid adenomata are palpable. Seldom, too, is an adenoma of sufficient size and in suitable position to distort the x-ray image of an esophagram or produce a mediastinal shadow.

In mild hyperparathyroidism clinical signs and indications are often incon-

spicuous and frequently can be elicited only by intensive questioning. These include symptoms due to hypercalcemia per se consisting of polydipsia, polyuria, muscular weakness, hypotonicity, hyporeflexia, anorexia, nausea, and vomiting. At times gastrointestinal symptoms may predominate, as in the second case described, and the possibility of hyperparathyroidism may be overlooked. Thus, in the absence of diagnostic signs and symptoms, an aroused suspicion of the possibility of hyperparathyroidism must be confirmed by laboratory studies.

When hyperparathyroidism exists an elevated serum calcium and a low serum phosphorus is present. These changes may be obscured, however, by other variables such as the presence of hypoproteinemia, impaired renal function, transient normocalcemic intervals (which occur in the less advanced forms of the disease), and the age of the patient.

Calcium exists in the serum as protein bound and ionic or free calcium. Only the ionic calcium increases in hyperparathyroidism but, unfortunately, the routine laboratory determination is the total of the two forms present. Thus in hypoproteinemia where the protein bound calcium is low, the ionic calcium may be elevated abnormally and yet the laboratory report may indicate a normal serum calcium level. Hence, evaluation of the protein level is necessary before ruling out hyperparathyroidism on the basis of a reported normal serum calcium level. It is of further value in recognizing a high total serum calcium level caused by an excessively high total protein such as occasionally occurs in multiple myeloma.

As has been mentioned previously, the low serum phosphorus level of hyperparathyroidism is the most reliable single clue to the diagnosis. A level below 2.5 to 3.3 mg. per cent almost invariably is present unless renal failure has occurred. Diminished renal function is a common secondary complication of prolonged hyperparathyroidism and is induced by the hypercalciuria which leads to nephrocalcinosis. With renal failure phosphorus retention occurs and, even in the presence of pronounced hyperparathyroidism, the serum phosphorus level may be normal. Hence, when the disease is suspected and the serum phosphorus is not low, impaired renal function may assist in explaining the absence of a low serum phosphorus.

An estimate of renal function is also of value in differentiating the secondary parathyroid hyperplasia due to advanced renal failure from primary hyperparathyroidism with renal calcinosis. In primary hyperparathyroidism renal function usually is impaired less seriously; however, the two conditions are occasionally indistinguishable without exploration of the parathyroid glands.

The age factor is important in children suspected of having hyperparathyroidism. During growth normal serum phosphorus levels may be 50 to 100 per cent above normal and this normal variation must be appreciated in evaluating serum phosphorus levels in children.

The Sulkowitch test is quantitative for urine calcium, demonstrating an excess of calcium in the urine in hyperparathyroidism. Since the test may be intermittently positive, a single negative value does not eliminate the possibility of hyperparathyroidism. It is pertinent to appreciate the multiple disease

states not embodying parathyroid function which cause a positive reaction in the Sulkowitch test.

In the first case presented, the diagnosis of hyperparathyroidism was suspected initially because of recurrent renal calculi and confirmed by the elevated serum calcium and low serum phosphorus. Of interest is the second series of calcium determinations of 10.3 and 12.4 mg. per cent in the presence of a depressed total protein of 5.2 Gm. per cent. With correction for the low total proteins, the calcium values are strikingly elevated from 12.0 to 14.0 mg. per cent. The constant depression of the serum phosphorus to 2.5 and below emphasizes the value of this determination as the more important diagnostic feature.

Case 2 clearly demonstrates a number of the variables which modify clinical and laboratory diagnosis of hyperparathyroidism. The symptoms of weakness, hypotonia and hyporeflexia were present but disappeared within 72 hours after removal of the parathyroid adenoma. It is interesting to speculate on the relationship of the gastrointestinal symptoms and the duodenal ulcer to the hyperparathyroidism. Refractory for more than 10 months to intensive ulcer management, the gastrointestinal symptoms and x-ray evidence of ulcer crater disappeared soon after the hyperparathyroidism had been corrected surgically. Recently other authors have noted cases of hyperparathyroidism associated with severe gastrointestinal symptoms and peptic ulcer.[8,9] The relationship appears to be more than coincidental in this case.

Because of the coexistent hypoproteinemia, the total serum calcium levels ranged from 10.4 to 11.5 mg. per cent. By assuming normal blood proteins, the degree of hypercalcemia became more intense. Using the chart of McLean and Hastings[10] which permits for this correction, the adjusted blood calcium values were 12.0 and 13.5 mg. per cent. The constancy of the low range of the serum phosphorus from 1.3 to 3.3 mg. per cent emphasizes the unexcelled significance of a low serum phosphorus in the diagnosis of the hyperparathyroidism. Variations in the Sulkowitch test also occurred which demonstrate its limitations as a diagnostic criterion.

Summary

The foregoing cases illustrate the importance of regarding hyperparathyroidism with suspicion when accompanied by recurrent renal calculi, hypotonia, hyporeflexia, weakness and gastrointestinal symptoms, refractory to intensive therapy. The basic physiology of hyperparathyroidism has been reviewed. Alterations in the anticipated serum calcium and serum phosphorus levels due to such variables as hypoproteinemia, depressed renal function, fluctuations in the reported laboratory studies, and the influence of age have been discussed and demonstrated. An attempt has been made to emphasize a depressed serum phosphorus as the most valuable single diagnostic determinant in obscure hyperparathyroidism.

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