9-1964

Primary Hyperparathyroidism With Hypercalcemia: Twenty-eight Years Before Treatment

A. Robert Arnstein

William S. Haubrich

Boy Frame

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation

Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol12/iss3/5

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons. For more information, please contact acabler4@hfhs.org.
PRIMARY HYPERPARATHYROIDISM WITH HYPERCALCEMIA
TWENTY-EIGHT YEARS BEFORE TREATMENT

A. ROBERT ARNSTEIN, M.D.,* WILLIAM S. HAUBRICH, M.D.,** AND
BOY FRANE, M.D.*

THE COURSE OF PRIMARY hyperparathyroidism may be quite prolonged. Cases with histories of renal lithiasis dating back 20 or more years are not uncommon. However, early biochemical evidence of parathyroid hyperfunction is usually lacking in patients with remote histories. The following patient was seen here for the first time in 1935 with kidney stones and hypercalcemia. She finally underwent parathyroidectomy in 1963 after 28 relatively healthy intervening years.

CASE REPORT

E. M., a 54-year-old white married female, was first seen at this hospital in 1935 at age 26 because of right-sided abdominal distress for five years, occasional nocturia and occasional headache. There were no skeletal symptoms. Family history was unremarkable. Physical examination was normal; the blood pressure was 116/56. Laboratory data included a hemoglobin of 12.8 gm. per cent and a white cell count of 9,700. The urinary specific gravity was 1.015, the urine contained small amounts of protein and a few red blood cells were in the sediment. The serum calcium was 12.2 mgm. per cent and the serum inorganic phosphorus was 2.7 mgm. per cent. An abdominal film revealed bilateral nephrolithiasis and the patient underwent a left nephrolithotomy.

In 1943 she returned because of three years of constant left costovertebral angle discomfort with intermittent exacerbations. Her only other significant complaint was chronic constipation. Physical examination was again normal with a blood pressure of 130/85. There was + proteinuria, the serum calcium was 11 mgm. per cent and the inorganic phosphorus was 2.1 mgm. per cent with an alkaline phosphatase of 2.4 Bodansky units. X-rays showed recurrent left nephrolithiasis and a left pyelolithotomy was done.

She was not seen again until July, 1963, at age 53, when she sought advice because of progressive left-sided backache. Other symptoms included ulcer-like epigastric distress, abdominal bloating, eructation and flatulence, and occasional nausea. Her appetite was good, she was gaining weight, and denied constipation. She reported an increased urinary volume with occasional nocturia. There were no musculo-skeletal complaints. The care of her invalid husband over the preceding five years had been emotionally, but not physically, taxing. On physical examination she was moderately obese. The blood pressure was 180/100. Positive findings included a left lower thyroid nodule, cardiac enlargement with an apical pansystolic murmur, an apical mid-diastolic rumbling murmur and an early diastolic third sound characteristic of an opening snap. In the out-patient department, serum calcium was 11.6 mgm. per cent (normal range 9-11 mgm. per cent) and an intravenous pyelogram disclosed multiple left renal calculi. She was admitted in October, 1963, for further evaluation.

*Fifth Medical Division.
**Division of Gastroenterology.
A series of serum calcium determinations ranged from 10.2 to 11.9 mgm. per cent with an average value of 11.1 mgm. per cent (Table 1). Serum phosphorus determinations ranged from 1.8 mgm. per cent to 2.5 mgm. per cent with an average of 2.1 mgm per cent (normal range 2.5-4.0 mgm. per cent). The alkaline phosphatase was 2.0 Bodansky units; serum creatinine, 0.8 mgm. per cent; urinary calcium, 100 mgm./24 hours, and TRP was 69 per cent. A 12 hour overnight gastric aspiration yielded 36 mEq. HCl in 700 ml. of gastric juice. Serum protein electrophoresis and serum CO₂ combining power were normal. Skeletal x-ray survey disclosed generalized bony demineralization but there were no cystic changes, no subperiosteal erosion of phalanges or enlargement of sella turcica. Barium swallow and upper gastrointestinal examination revealed a small hiatus hernia but no peptic ulcer. The cardiac silhouette was enlarged and the electrocardiogram was compatible with left ventricular hypertrophy. Lacking evidence for either endocrine adenomatosis or a non-parathyroid cause for the hypercalcemia and hypophosphatemia, a clinical diagnosis of primary hyperparathyroidism was made. She was also thought to have rheumatic mitral valvular disease.

Neck exploration was performed on November 8, 1963, by Dr. Melvin A. Block. Three of four glands identified were slightly enlarged. A subtotal parathyroidectomy was done consisting of the removal of two and one-half of the three enlarged glands. The fourth normal appearing gland was left intact. Her postoperative course was complicated by a pulmonary embolus and thrombophlebitis of the right calf treated with anticoagulants.

Four months postoperatively the patient reported that she has felt generally improved. She has had no more abdominal pain or bloating, although nocturia continues. Since surgery, serum calcium, as summarized in table 1, has been normal or slightly low.

Pathologically, the resected parathyroid tissue was interpreted by Dr. Robert C. Horn as mild chief cell hyperplasia.

**DISCUSSION**

A review of the English language literature and correspondence with a number of investigators of broad experience in parathyroid disease indicate that this patient, with hypercalcemia on two occasions 28 years apart, represents the longest recorded documentation of primary hyperparathyroidism.

The history of kidney stone and hypercalcemia 28 years before surgical treatment leaves little doubt that this patient did, indeed, have hyperparathyroidism at that time. The calcium method in use here in 1935 was that of Clark and Collip with a laboratory error estimated at 5-10 per cent. The normal range for the laboratory at that time was 9-11 mgm. per cent and discussion with two individuals working then in the clinical laboratory assures us that 12.2 mgm. per cent should be considered a distinct elevation. Other than laboratory error, a mechanical one may enter at the time of venipuncture as a result of prolonged venous stasis and in vivo ultrafiltration, which, in the course of five minutes may raise the serum calcium concentration as much as 1 mgm. per cent.

These considerations aside, the clinical evolution of a rather typical case of hyperparathyroidism has influenced us to accept the original calcium determination as a true elevation. The availability of this early serum calcium value, therefore, provides objective support for a clinical assumption that, in all likelihood, would have been made without it.

Prior to this report, the longest documented hypercalcemia in primary hyperparathyroidism of which we know is 20 years in two patients of Keating and 16
HYPERPARATHYROIDISM

years in one of the Massachusetts General Hospital series.\(^4\) Clinical estimation, based only on the duration of symptomatic renal lithiasis, provides evidence for courses as long as 35, 36, 39 and 44 years.\(^3\) Cases of primary hyperparathyroidism with long-standing renal lithiasis usually do not have clinically significant bone disease, the presence of which tends to result in earlier diagnosis.\(^7\)

Although cases with long histories are not uncommon, the course of all clinical forms of primary hyperparathyroidism is becoming shorter and milder due to heightened awareness of the clinical consequences of hypercalcemia.\(^5,^9\) In fact, a point has been reached today wherein the "borderline case" is an increasingly frequent clinical problem. Diagnostic uncertainty in these cases arises from unpredictable day-to-day fluctuations in serum calcium, a paucity of symptoms, and other chemical and physiologic indices of parathyroid function which are, often, completely normal. Repeated and prolonged observation of serum calcium may be necessary before neck exploration is recommended with confidence. The patient reported here exemplifies this situation in that her serum calciums hovered just above and below the upper limit of normal (Table I). Diagnosis was abetted, however, by a persistently low serum inorganic phosphorus and a low value for per cent TRP.

Do patients with long histories, like the woman in this report, have intermittent or chronic, mild parathyroid hyperactivity? The possibility of intermittent parathyroid hyperfunction has been suggested by Whitby\(^8\) and Veenema.\(^11\) This idea is supported

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Calcium mgm. %</th>
<th>Serum Phosphorus mgm. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1935: Aug. 23</td>
<td>12.2</td>
<td>2.7</td>
</tr>
<tr>
<td>1943: Aug. 9</td>
<td>11.0</td>
<td>2.1</td>
</tr>
<tr>
<td>1963: Sept. 19</td>
<td>11.6</td>
<td></td>
</tr>
<tr>
<td>Oct. 14</td>
<td>10.9</td>
<td>2.1</td>
</tr>
<tr>
<td>16</td>
<td>10.2</td>
<td>1.8</td>
</tr>
<tr>
<td>17</td>
<td>11.9</td>
<td>2.0</td>
</tr>
<tr>
<td>18</td>
<td>11.2</td>
<td>2.3</td>
</tr>
<tr>
<td>21</td>
<td>11.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Nov. 6</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>8 Subtotal Parathyroidectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>8.4</td>
<td>3.5</td>
</tr>
<tr>
<td>11</td>
<td>9.1</td>
<td>2.3</td>
</tr>
<tr>
<td>12</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>1964: Jan. 20</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Mar. 2</td>
<td>8.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

329
ARNSTEIN, HAUBRICH AND FRAME

by the reports of cyclic symptoms\textsuperscript{32,33} and spontaneous improvement of osteitis fibrosa cystica.\textsuperscript{34} However, most examples of sustained clinical and chemical remission are related to parathyroid tumor necrosis.\textsuperscript{15,16,17,18} An interesting exception to this may be case three of Lemann and Donatelli,\textsuperscript{19} whose remission lasted at least one month, but in whom the area of tumor necrosis was reported to be rather small. On the other hand, Keating feels that serum calcium has remarkable stability when documented with repeated determinations over periods as long as 20 years.\textsuperscript{3,4} His observations, therefore, would favor a situation of mild chronic hyperactivity. The data on the patient presented here is inconclusive in this respect, but there is one other patient in the series from this hospital who displays this long-term stability of serum calcium. She is, incidentally, an example of recurrent parathyroid adenoma reported elsewhere,\textsuperscript{20} whose serum calciums during a 14 year period ranged between 11.4 and 13.7 mgm. per cent. These determinations were done on follow-up visits, but she had no symptoms that could be attributed to hypercalcemia. These experiences, together with the lack of any well-documented cases of clinical and chemical intermittency, fortify our belief that most cases of long duration have chronic hyperactivity of low intensity.

Another interesting facet of long-standing hyperparathyroidism comes from a consideration of the variability of the individual response to parathyroid hyperfunction. In addition to the patient reported here, there are two others in the Henry Ford Hospital series with histories of renal calculus disease of 19 and 25 years duration respectively. At the time of treatment, none of these patients had evidence of skeletal involvement or renal functional impairment. Mean serum calcium levels were 11.1 mgm. per cent in two and 12.3 mgm. per cent in the third.

In contrast to this relatively benign situation, is the occasional patient with similar serum calcium levels who gets into trouble in a short period of time with symptomatic bone disease. In fact, Dent feels that patients can be clearly separated into two clinical groups; \textit{i.e.}, those with and those without skeletal involvement.\textsuperscript{21} He suggests that the clinical differences between these groups, which includes a shorter course and a tendency to more renal impairment in the group with osteitis, may result from differences in the potency of hormone secreted or in the end-organ responsiveness to a single hormone. A recent study by Hodgkinson would suggest, however, that differences among patients with primary hyperparathyroidism are those of degree rather than kind; that there is no sharp line of demarcation between patients with and those without bone disease.\textsuperscript{22} Nevertheless, it does appear that some patients resist, more successfully than others, the effects of increased levels of parathyroid hormone. This suggests that a variable interplay of undefined biologic factors may act to determine end-organ susceptibility to parathyroid hormone as well as the metabolic response of tissues to hypercalcemia. This is, indeed, an area of great challenge in the further understanding of the pathophysiology of primary hyperparathyroidism.

330
HYPERPARATHYROIDISM

SUMMARY

A patient has been presented with primary hyperparathyroidism due to chief cell hyperplasia with hypercalcemia documented 28 years prior to treatment. The case lends objective support to the widely held belief that primary hyperparathyroidism may have a course of several decades, much of which is subclinical. Certain aspects of the nature of primary hyperparathyroidism of long duration have been briefly discussed.

REFERENCES

5. Reiss, E. Personal communication. 1963.
14. Linden, O.: Case of ostitis fibrosa generalisata with well-marked tendency to spontaneous cure, Acta Radiol. 15:202, 1934.