

Primary hyperparathyroidism— A clinical study

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Summary

Fifteen patients with primary hyperparathyroidism were seen over a 14-year period in the University Hospital, Kuala Lumpur, Malaysia. Seven patients presented predominantly with bone disease, 5 with urolithiasis and 3 patients were asymptomatic. Other complications included acute psychosis, pancreatitis, myopathy and renal tubular acidosis. One patient had multiple endocrine adenomatosis (MEA) Type I syndrome. This paper highlights the severe and varied effects of undiagnosed hyperparathyroidism.

Key words: Multiple endocrine adenoma, osteitis fibrosa, primary hyperparathyroidism, urolithiasis.

Introduction

Primary hyperparathyroidism is a condition with protean manifestations and should be considered in patients with hypercalcaemia, recurrent kidney stones, diffuse osteoporosis or peptic ulcer disease. Patients with hypercalcaemia may present with vague constitutional symptoms, anorexia, lethargy, proximal muscle weakness or polydipsia and polyuria. Current practice of routine multiphasic blood testing has uncovered hypercalcaemia in many asymptomatic patients. Conversely when serum calcium estimation is not routinely done primary hyperparathyroidism may remain undetected. This study reviews the clinical features of our patients with primary hyperparathyroidism, to show how insidious and debilitating a condition it may be.

Materials and Methods

Records of patients with primary hyperparathyroidism managed at the University Hospital, Kuala Lumpur, Malaysia, over a fourteen year period from 1972 to 1985 were reviewed. Patients were considered to have primary hyperparathyroidism when there was (i) typical clinical and radiological features consistent with the disease, (ii) raised serum calcium in the absence of other causes for the hypercalcaemia, (iii) increased serum immunoreactive parathyroid hormone concentrations (when available) and (iv) histological diagnosis of parathyroid adenoma or hyperplasia.

Hypercalcaemia was defined as serum calcium greater than 2.8 mmol/L after correction for serum albumin. Blood samples for calcium were taken without venostasis. All serum calcium estimations were done in the Central Diagnostic Laboratory of the Hospital using a colorimetric method (o-cresolphthalein; Abbott Laboratories). Serum immunoreactive parathyroid hormone was measured by courtesy of Professor S. Posen of Sydney, Australia, by radioimmunoassay. Levels greater than 0.50 ng/ml were considered raised.

Results

Fifteen cases of primary hyperparathyroidism were diagnosed over the fourteen year period. The mean age was 36.3 years; ten patients (67%) were in the second and third decades of life. The sex distribution was nearly equal (males 8, females 7). Of the 15 patients, six were Chinese, five Indians, two Malays and one Caucasian.

Table I
Clinical Features and Laboratory Data of the Fifteen Patients

Patient	Sex	Age	Clinical Features	*Serum Values at Presentation			
				Ca ⁺⁺ mmol/L	PO ₄ mmol/L	ALP i.u./L	PTH ng/ml
1	F	24	urolithiasis; asymptomatic bone disease	3.1	0.4	280	—
2	F	36	osteitis fibrosa	3.4	0.5	420	1.7
3	F	34	osteitis fibrosa, nephrocalcinosis	3.1	0.4	> 600	—
4	M	49	hypertension; duodenal ulcer	3.4	0.5	100	—
5	F	44	urolithiasis, psychosis, hypertension	2.9	0.5	100	—
6	M	36	urolithiasis, hypertension	3.2	0.5	80	—
7	M	26	osteitis fibrosa; mandible removed	3.1	0.5	> 350	1.45
8	F	44	osteitis fibrosa (maxillary cyst); proximal myopathy	2.8	0.4	350	1.4
9	F	24	osteopenia, proximal myopathy and renal tubular acidosis	2.9	0.6	> 350	—
10	M	32	osteopenia with vertebral fracture	2.9	0.5	> 350	—
11	F	27	osteitis fibrosa, nephrocalcinosis and pancreatitis, proximal myopathy, hypertension	3.1	0.6	> 350	8.0
12	M	34	urolithiasis, hypertension	3.5	0.5	250	0.96
13	F	29	asymptomatic	3.2	0.6	90	1.1
14	M	53	multiple endocrine adenomatosis Type 1	3.1	0.7	150	0.64
15	M	52	urolithiasis, hypertension	2.8	1.2	100	0.94

* Normalised serum albumin

Lenged: PTH — Parathyroid Hormone levels
ALP — Alkaline Phosphatase

The duration of symptoms before the diagnosis of hyperparathyroidism ranged from 2 weeks to 9 years (Fig. 1) with a mean of 4.0 years. Patients with bone disease appeared to present earlier than those with urolithiasis. The mean duration of symptoms of patients with predominantly bone disease was 2.8 years while that of patients with predominantly urolithiasis was 5.2 years.

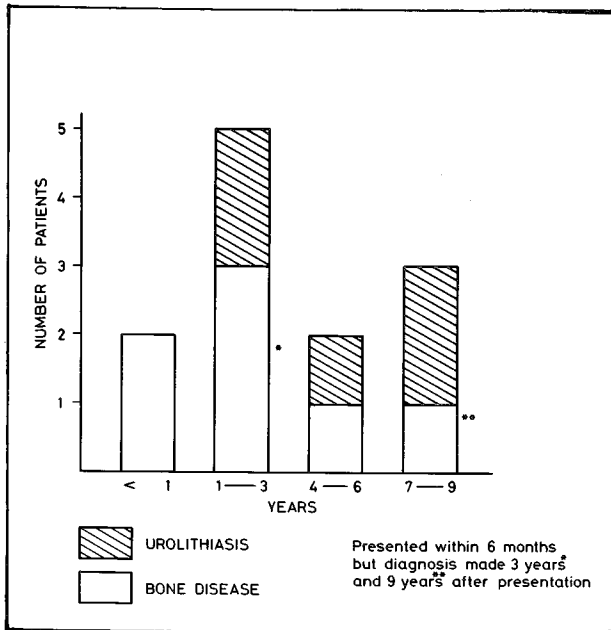


Fig. 1
Duration of symptoms before the diagnosis of hyperparathyroidism.

The presenting complaints of the patients are shown in Table II. Seven patients presented with bone pains or bone swelling, five presented with renal colic with or without symptoms of urinary tract infection. Two patients presented with more than one complaint. Patient 5 had acute psychosis and renal colic while patient 11 presented with severe bone pains, pancreatitis and features of acute hypercalcaemia.

Table II
Presenting Complaints of Primary Hyperparathyroidism

	Our Report	Mundy et al (1980) (5)	Hellstrom and Ivemark (1962) (4)
Presentation	N = 15	N = 111	N = 138
Renal Colic	33% (5)	7%	79%
Bone pains/and swelling	47% (7)	—	20%
Psychiatric disorder	7% (1)	5%	—
Gastrointestinal symptoms	7% (1)	14%	—
Symptoms of hypercalcaemia	7% (1)	8%	—
Accidental	20% (3)	57%	—

N = total number of cases

Numbers in parentheses are the actual number of patients.

Three patients had no obvious manifestation of hyperparathyroidism. Patient 4 was a 49-year-old Caucasian man who was being investigated for hypertension and epigastric pain. A parathyroid tumour was removed at surgery. Patient 14 was found to have hyperparathyroidism as part of the syndrome of multiple endocrine adenomatosis type I. He presented with symptoms of fasting hypoglycaemia which was found to be due to an insulinoma. He was also acromegalic. A third patient (Pt. 13) while being investigated for proteinuria was noted to have persistently elevated serum calcium levels of 3.1 to 3.3 mmol/L with raised serum parathyroid hormone level of 1.1 ng/ml.

Bone changes were common and severe in these patients. Five had florid changes of osteitis fibrosa cystica. All five patients had subperiosteal erosions in the skull and phalanges of the hands and cysts in the long bones of the legs. One patient (Pt. 7) developed a pathological fracture of the left femur. Three patients had huge bone cysts of the maxilla (Pt. 8, Fig. 2), mandible (Pt. 7, Fig. 3), and pelvic bone (Pt. 11). Patient 7 had his jaw and patient 11 the right iliac bone excised three and nine years previously for a mistaken diagnosis of osteoclastoma.

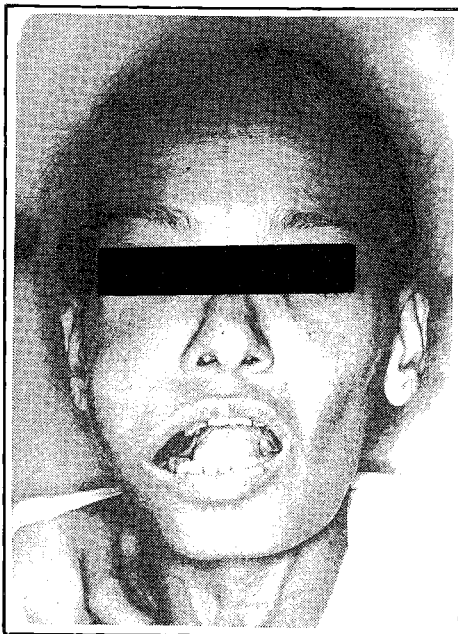


Fig. 2
Swelling over the right maxilla (Pt. 8)

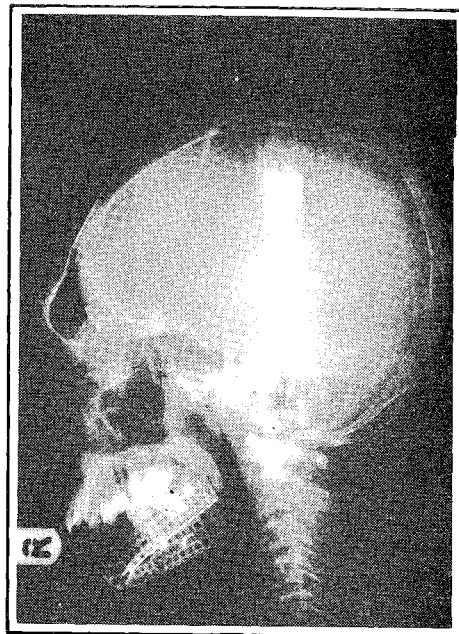


Fig. 3
Mandible removed and replaced with a prosthesis (Pt. 7)

Two patients with severe bone pains and generalized osteopenia with compression fracture of the twelfth thoracic vertebra (Pt. 10), and severe proximal muscle weakness with osteomalacia and renal tubular acidosis (Pt. 9). Two of the seven patients with bone disease had silent nephrocalcinosis. Five patients had renal colic from urolithiasis. All had passed stones and repeated episodes of urinary tract infection. Only one of these five patients had radiological bone disease with subperiosteal erosions of the phalanges. None had clinically symptomatic bone disease.

Patient 5 had renal calculi and presented with psychosis which improved slowly following parathyroidectomy. Two other patients had mild depression. Six patients had persistent high blood pressure (B.P. > 140/100), three were hypertensive before the diagnosis of primary hyperparathyroidism was made. Only one patient (Pt. 11) had symptomatic chronic pancreatitis. Pancreatic calcifications were noted in the abdominal X-rays of two other patients (Patients 1 and 6) who were asymptomatic. Band keratopathy was not seen in any of the patients.

The corrected serum calcium levels were more than 2.8 mmol/L in all the 15 patients while serum phosphate levels were below normal (0.6 mmol/L) in 14. Serum alkaline phosphatase was markedly raised in the seven patients with bone disease while serum parathyroid hormone levels were increased in all the eight patients on whom it was done.

Eleven patients underwent neck exploration and parathyroidectomy. Ten patients fulfilled more than one of Purnell's criteria for parathyroidectomy.¹ These included high serum calcium levels > 2.75 mmol/L (all patients), urinary calculi with recurrent urinary tract infections (3 patients), severe bone disease (6 patients) and one patient with both bone disease and severe gastrointestinal complaints. Three patients (Patients 9, 10, 11) had accurate preoperative localization of their parathyroid adenomas by ultrasonography. Other investigations such as selective venous sampling for parathyroid hormone assay, arteriography or selenomethionine scanning were not done. At operation, single adenomas were found in all the patients. 90% of the adenoma were located in the inferior lobe.

Discussion

Primary hyperparathyroidism was previously considered to be rare.² With greater awareness of its diverse manifestations and the availability of more accurate and inexpensive methods of measuring serum calcium and serum parathyroid hormone many asymptomatic cases have been recognised. The condition became even more common since the introduction of routine biochemical screening in the late 1960's. A population study in Rochester showed a significant rise from 7.8 per 100,000/year to 27.7 per 100,000/year.³ The number of cases in this report may be small since routine serum calcium estimation is not done at our centre.

The age distribution of our patients is comparable to the report of Hellstrom and Ivemark⁴ which was carried out prior to routine multiphasic blood testing. As in their study, all our patients were below sixty years of age. By contrast, a later study by Mundy et al⁵ showed that 75% of the patients were over sixty years of age. Many were asymptomatic and diagnosis was made based on the laboratory detection of hypercalcaemia.

The condition appears more common in females, with a male to female ratio of approximately 4 to 1.^{4,5} Amongst our patients however the sex ratio was equal. It is unclear why there is no female preponderance amongst our patients. This may be due to the small number of patients.

The mode of presentation of our patients is comparable to that of the patients reported by Hellstrom and Ivemark but contrasted markedly with that reported by Mundy et al (Table II). In our study as in the study reported by Hellstrom and Ivemark, the majority of patients were symptomatic, with bone disease and urolithiasis being the most common presentations. However in the study by Mundy et al, more than half the patients were asymptomatic and were detected incidentally. Of the patients who were symptomatic in this latter group, gastrointestinal symptoms were the most common presentation. The difference in the mode of presentation is probably due to the early diagnosis of primary hyperparathyroidism in the group of patients studied by Mundy et al.

In this study we have noted that patients with predominantly bone disease presented earlier and seemed to be spared from significant renal disease, supporting the observations of Mallette et al.⁶ The latter also noted that patients with bone disease had large parathyroid adenomas. This was noted in 2 of our patients who had adenomas weighing greater than 8.0 grams each (Pts. 3 and 11).

Two of our patients had diffuse osteopenia without any changes of osteitis fibrosa. It has been noted that osteitis fibrosa cystica is now uncommon and that diffuse osteopenia is more frequently seen.⁷ In a recent report⁸ of 87 patients, X-ray changes of osteopenia were found in the spine in 21% of patients and in the hands in 36%. Evidence of osteitis fibrosa cystica was noted in only 9% of patients. In another report,⁹ 14 patients had diffuse osteopenia of the spine and vertebral crush fractures as with patient 11 in our study. It is still not clear why there has been a changing pattern of skeletal involvement from osteitis fibrosa cystica to diffuse osteopenia.

Renal tubular acidosis (RTA) as seen in patient 9 is a rare complication of primary hyperparathyroidism. Patients may develop distal RTA as a result of nephrocalcinosis.¹⁰ However proximal tubular defects in the absence of nephrocalcinosis have been noted to be common.⁷ It is thought that the parathyroid hormone may have a direct effect on the renal tubules.⁷

A case of multiple endocrine adenomatosis (MEA) Type I or Wermer's Syndrome was seen amongst our patients. Hyperparathyroidism is also a feature of MEA Type II. Watson¹¹ reported 10 cases of pluriglandular syndromes among his first 350 patients with parathyroid tumours. The diagnosis of MEA should be considered if more than one family member has primary hyperparathyroidism.

In this review of 15 patients, there are examples of severe disease amongst the patients. This is likely due to a delay in clinical diagnosis and partly from inadequate support. It is hoped that this paper will remind clinicians of the devastating results of undiagnosed hyperparathyroidism.

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References

1. Purnell DC, Smith LH, Scholz SA, Elveback LR, Annaud CD: Primary hyperparathyroidism: a prospective clinical study. *Am J Med*, 1971; 50 : 670 - 678.
2. Keating FR, Cook EN. The recognition of primary hyperparathyroidism. An analysis of
3. Heath H III, Hodgson SF and Kennedy MA. Primary hyperparathyroidism: incidence, morbidity and potential economic impact in a community. *N Engl J Med*, 1980; 302 : 189-193.
4. Hellstrom J, Ivermark BL. Primary hyperparathyroidism: clinical and structural findings in 138 cases. *Acta Clin Scand* 1962; 294: suppl 1-113.
5. Mundy GR, Cove DH, Fischen R. Primary hyperparathyroidism: changes in the pattern of clinical presentation. *Lancet*, 1980; i:1317-1320.
6. Mallette LE, Bilexikian JP, Heath DA, Annbach GD. Primary hyperparathyroidism: clinical and biochemical features. *Medicine*, 1974; 53 : 127-146.
7. Hábener JF, Potts JT Jr. Clinical features of primary hyperparathyroidism. In: Degroot LT et al (eds), *Endocrinology*. Grune & Stratton, 1979; 693-701.
8. Genant HK, Banon JM, Straus FH II, et al. Osteosclerosis in primary hyperparathyroidism. *Am J Med*, 1975; 59 : 104-113.
9. Dauphine RT, Riggs BL, Scholz DA. Back pain and vertebral crush fractures: an unemphasized mode of presentation for primary hyperparathyroidism. *Ann Intern Med*, 1975; 83 : 365-367.
- 10 Morris RC Jr. Renal tubular acidosis. *N Engl J Med*, 1981; 304 : 418-419.
- 11 Watson L. Primary hyperparathyroidism. *Clin Endocrinol Metab*, 1974; 3 : 211-235.