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Diagnosis and Treatment of Primary Hyperparathyroidism

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Summary. The leading symptom of primary hyperparathyroidism is renal lithiasis which was present in 64 of 100 cases, whereas bone disease was noted in 11 per cent only. The diagnosis of primary hyperparathyroidism is generally made on the basis of raised serum levels of calcium and of immunoreactive parathyroid hormone (PTH). With antibodies detecting primarily COOH-terminal fragments of intact PTH-(1-84) there was an almost total discrimination of serum levels of PTH in normal subjects and in patients with primary hyperparathyroidism. Serum PTH was in the upper normal range in only 5 per cent of 128 patients with surgically verified hyperparathyroidism, whereas PTH was normal or undetectable in 35 hypercalcaemic patients with tumours unrelated to the parathyroid glands. A comparable discrimination of patients with primary hyperparathyroidism from normal subjects can be achieved with the measurement of the urinary cyclic adenosine 3', 5' -monophosphate excretion, provided it is related to the glomerular filtration rate. With the measurement of the urinary excretion of calcium and phosphate, on the other hand, there is a large overlap in control subjects and in patients with primary hyperparathyroidism.

The surgical removal of parathyroid tumours is the treatment of choice of primary hyperparathyroidism. In the routine preoperative evaluation, we do not recommend PTH measurements in the venous effluent of parathyroid tumours, since all parathyroid glands have to be surgically localized. In previously explored patients the interpretation of selective PTH measurements is difficult because of distorsion of the venous drainage from the parathyroid glands.

Key words: Calcium, Hyperparathyroidism, Parathyroid hormone.

The leading complications of primary hyperparathyroidism (pHPT) are nephrolithiasis and/or nephrocalcinosis (64% of 100 surgically verified patients) (11). Nephrolithiasis, on the other hand, is related to tumours of the parathyroid glands in 7% (range 1.3 to 16.8%) of 2,980 patients (16). Clinically noticeable involvement of the skeleton is much rarer. Osteitis fibrosa generalisata (Recklinghausen's disease) is practically no more existent. On radiological examination, we have visualized bone cysts and subperiosteal bone resorption in only 11% of 100 patients with pHPT using conventional techniques and in 42% with medical x-ray films for mammography (24). On quantitative histomorphometric analysis of biopsies from the iliac crest marked fibro-osteoclasia has only been demonstrated in 10% of 100 patients with pHPT (13, 28). Chondrocalcinosis, on the other hand, commonly occurs in pHPT (32% of 41 patients) (9, 31). Peptic ulcer disease does not seem to occur more frequently in pHPT than in control subjects with the exception of patients with multiple endocrine adenomatosis and Zollinger-Ellison syndrome (14, 29).

The most important screening finding is hypercalcaemia. Normocalcaemic hyperparathyroidism is extremely rare, unless patients suffer from vitamin D-deficiency or a disturbance of vitamin D-metabolism (e.g. nutritional vitamin D-deficiency, vitamin D dependent rickets, intestinal malabsorption and renal insufficiency), pseudohypoparathyroidism, or renal calcium loss (6, 7, 12, 18, 36). Tertiary hyperparathyroidism, if it does exist, cannot be distinguished from pHPT. Determination of the serum ionised calcium does not greatly enhance the discrimination of patients with pHPT from control subjects as compared to the measurement of the total calcium (Fig. 1). Total calcium may be increased in patients with hyperprotein-

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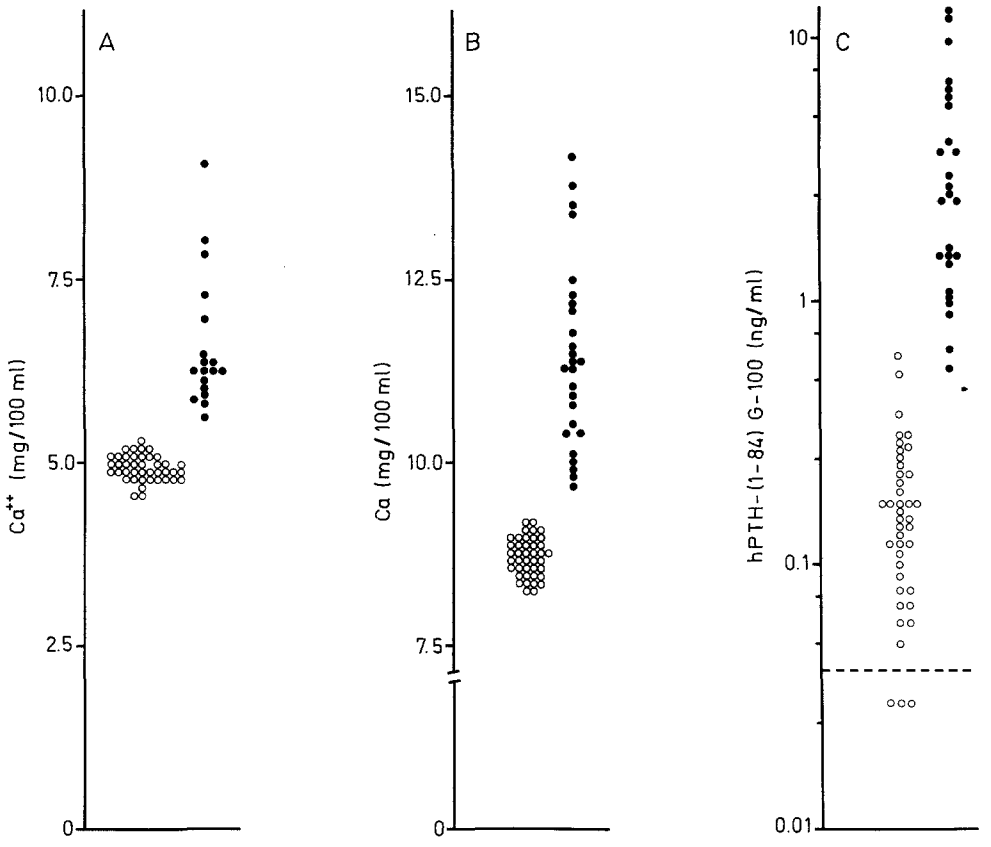

Fig. 1. Serum levels of ionised calcium (A), ethylene glycol bis (β-aminoethyl ether)-N, N' -tetra-acetate (EGTA) titratable calcium (B) and PTH (C-assay)(C) in control subjects (o) and in patients with pHPT (•). After Fischer et al. (17)

Table 1. Differential diagnosis of hypercalcaemia according to frequency of occurrence

1. Malignant tumours with or without skeletal metastases (ectopic hyperparathyroidism, secretion of prostaglandins), malignant haematological disorders such as multiple myeloma and malignant lymphoma
2. Primary (and tertiary) hyperparathyroidism
3. Oestrogen treatment of carcinoma of the breast
4. Hypervitaminosis D (or A)
5. Milk-alkali syndrome
6. Sarcoidosis
7. Immobilisation (Paget' s disease)
8. Treatment with thiazide diuretics
9. Treatment with lithium
10. Hyperthyroidism, acute Addison' s disease

aemia and multiple myeloma, while the serum ionised calcium is still within the normal range. The serum ionised calcium has to be measured using a calcium specific electrode; it cannot be calculated with confidence from the levels of serum proteins and the pH (23). pHPT can be suspected, if additional causes of hypercalcaemia have been ruled out (Table 1), and the diagnosis established with the measurement of the serum immunoreactive parathyroid hormone (PTH) level (2, 17, 19).

Intact PTH is a polypeptide hormone consisting of a single chain of 84 amino acids. Circulating PTH largely consists of fragments in addition to the intact hormone. The most abundant forms represent COOH-terminal fragments having molecular weights of 4, 000-7, 000. Radioimmunoassays using antibodies directed to COOH-terminal parts of human PTH-(1-84) (C-assay) are more suitable in discriminating patients with pHPT from control subjects than antibodies directed to the biologically active NH_2-terminal parts of the hormone (N-assay) (1, 17, 34). The large majority of patients with pHPT have raised levels of serum PTH when measured with a C-assay (Figs. 1, 2).

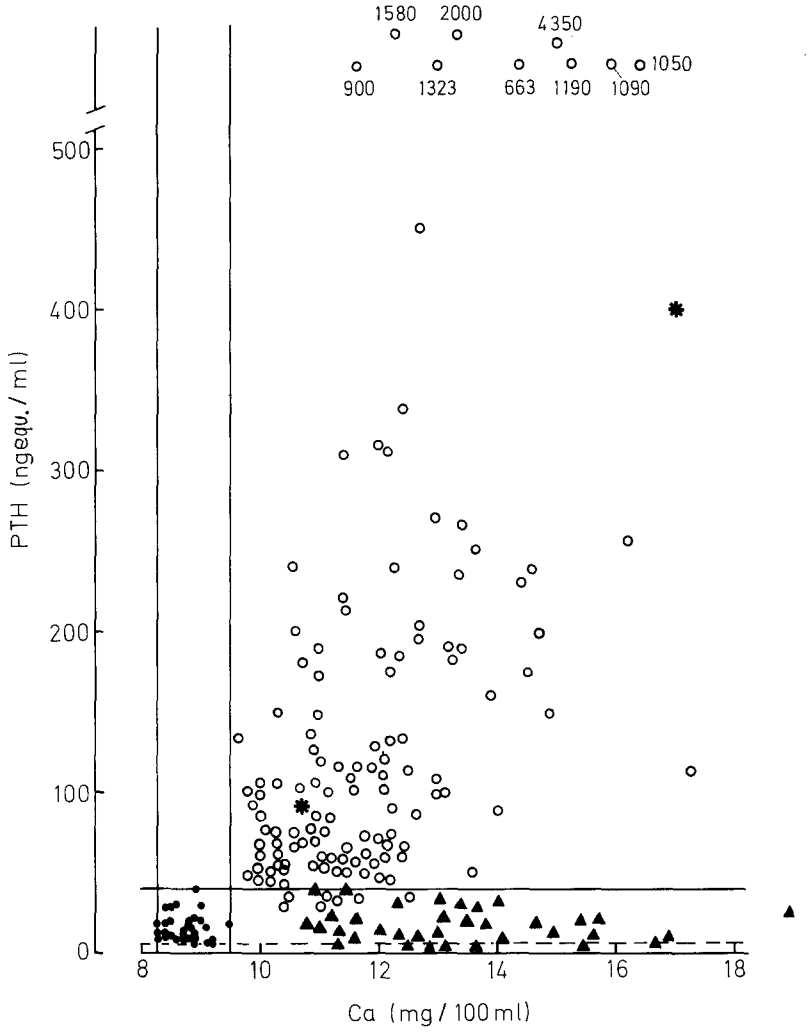

Fig. 2. Serum levels of PTH (C-assay) as a function of EGTA titratable calcium in control subjects (●), patients with pHPT (o), with malignant tumours unrelated to parathyroid glands (▲), and 2 patients with carcinoma of the scrotum and malignant lymphoma respectively (*). After Fischer et al. (19)

As shown in Figure 2 serum levels of PTH were raised in 95% of 128 patients with surgically proven pHPT and in the high normal range between 35 and 40 ng/ml (normal up to 40 ng/ml) in 5% of our patients. Serum levels of calcium were related to serum PTH levels. 35 patients with hypercalcaemia and malignant tumours unrelated to the parathyroid glands (e. g. bronchial and renal carcinoma, haematological disorders) had undetectable or normal PTH levels regardless of the absence or presence of bone metastases. In these patients there was no relation between the serum levels of PTH and of calcium (Fig. 2). The hypercalcaemia is caused in some of these patients by an ectopic production of PTH (3) or by an excess of prostaglandins (32); in the majority the pathogenesis of the hypercalcaemia is unknown. On the other hand, pHPT may be associated with other tumours; in two patients with a carcinoma of the scrotum and a malignant lymphoma respectively, hypercalcaemia was caused by concomitant pHPT levels (Fig. 2).

Whereas antibodies which are specific for determinants in the COOH-terminal parts of human PTH-(1-84) (C-assay) mainly recognise presumably biologically inactive PTH fragments in addition to the intact hormone, antibodies to the NH_2-terminal region or to synthetic human PTH-(1-34) (N-assay) largely recognize the biologically active intact PTH (1-84). Even so, using an N-assay, a smaller number of patients with pHPT have raised levels of circulating immunoreactive PTH than with the C-assay, and the N-assay appears diagnostically less useful than the C-assay (1, 17, 34). In view of the rather long half-life of circulating COOH-terminal fragments as compared to intact human PTH-(1-84) particularly in patients with chronic renal

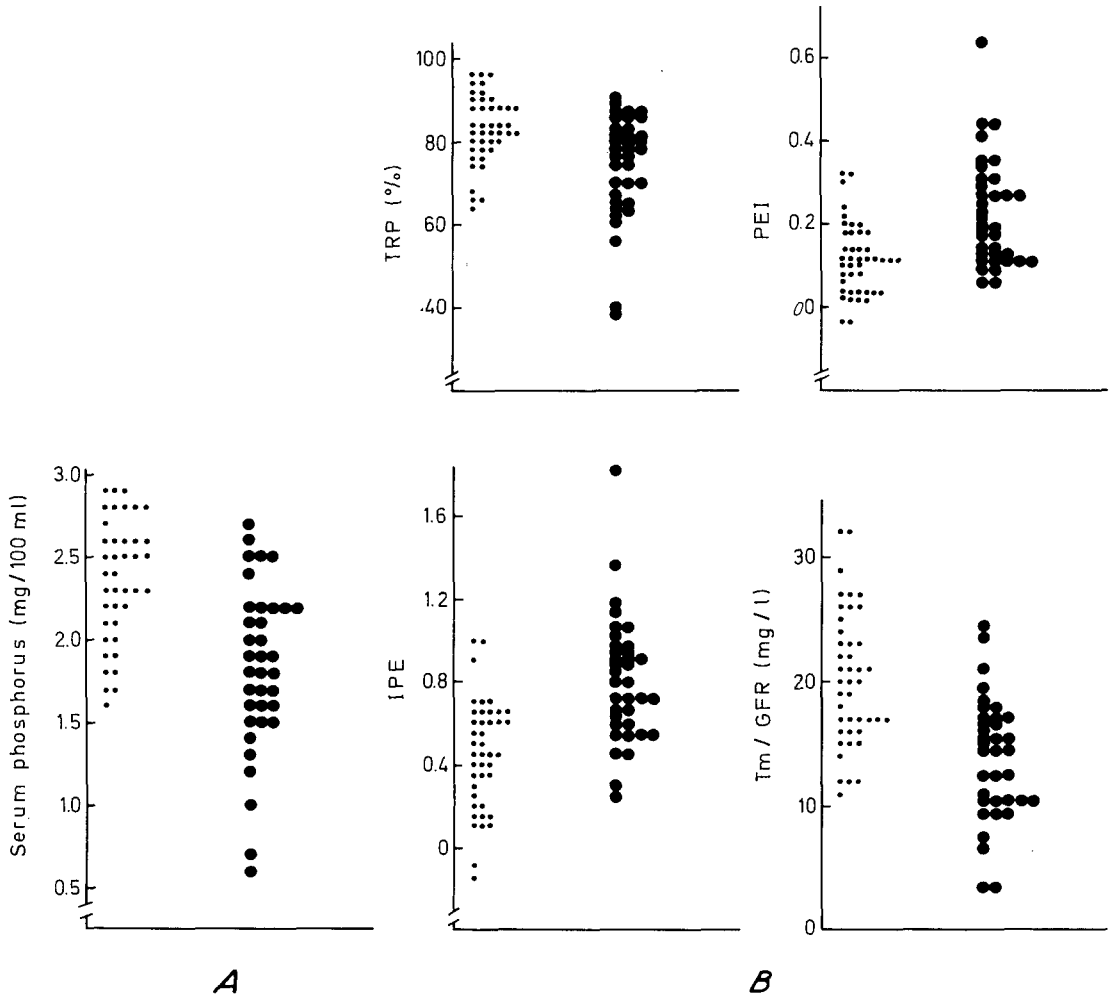

Fig. 3A and B. Serum levels of inorganic phosphorus (A) and parameters of urinary phosphate excretion (B) in control subjects (o) and in patients with pHPT (•). TRP, tubular reabsorption of phosphate; PEI, phosphate excretion index and IPE, index of phosphate excretion, after Nordin and Bulusu (27); Tm/GFR, maximal tubular reabsorption of phosphate after Bijovet (4). From Binswanger and Fischer (5)

insufficiency, the N-assay appears more suitable than the C-assay for the determination of changes of the secretion of PTH induced by various agents. This is particularly evident during calcium infusions or treatment with 1,25-dihydroxycholecalciferol, where a significant inhibition of serum PTH levels was only observed using an N-assay but not a C-assay (6, 20).

The N-assay is, furthermore, suitable for the measurement of PTH levels in veins draining the parathyroid glands. The localisation of abnormal parathyroid tissue is rather difficult and should not be routinely used, especially since in the large majority of patients tumours of the parathyroid glands are successfully removed by experienced surgeons. During surgical intervention all the parathyroid glands have to be explored because multiple adenomata or diffuse hyperplasia of all the glands do not infrequently occur. After unsuccessful surgical exploration of the parathyroid glands the interpretation of PTH measurements in the venous parathyroid effluent is particularly difficult in view of a distorted venous drainage. In these cases arteriography for parathyroid localisation may be helpful, especially when an adenoma is aberrant, such as in the mediastinum (15).

Recently, the measurement of the urinary cyclic 3', 5'-adenosine monophosphate excretion (cAMP) has been shown to be diagnostically useful, provided it is related to the glomerular filtration rate (GFR) (8, 33). Regardless of whether the nephrogenous cAMP excretion, which requires the measurement of plasma cAMP levels, or the urinary cAMP related to 100 ml GFR are determined in pHPT 90% of 57 patients exhibited pathologically raised cAMP excretion(8).

The urinary calcium excretion is raised in hypercalcaemic patients. The tubular reabsorption of calcium is increased in pHPT, but measurements are not sufficiently precise to be diagnostically useful. Normocalcaemic and normocalciuric (< 250 mg/24 h) primary hyperparathyroidism, if it does exist, is extremely rare; idiopathic hypercalciuria can be caused by raised intestinal calcium absorption or bone resorption, or a renal calcium loss (7, 25, 30).

Serum inorganic phosphorus and the various indices for the measurement of the urinary phosphate excretion (tubular reabsorption of phosphate; phosphate excretion index and index of phosphate excretion (27); maximal tubular reabsorption of phosphate (4)) are in a pathological range in less than half of the patients with pHPT (Fig. 3). A variable inhibition of the clearance of phosphate during calcium infusions has been used to evaluate the "autonomy" of PTH secretion of pHPT (21, 22); the determination of the response of serum PTH levels to calcium and/or EDTA infusions, however, is essential for the evaluation of parathyroid secretory function in pHPT (7, 26).

Bone remodelling is increased in pHPT when determined through a quantitative morphometric analysis of biopsies from the iliac crest; specific signs of fibroosteoclasia are only encountered in 10% of the patients with pHPT (13, 28). The evaluation of bone biopsies appears not be be essential for the diagnosis of pHPT.

The surgical removal of parathyroid tumours is the treatment of choice of pHPT. Non-operated patients may develop progressive nephrolithiasis, nephrocalcinosis, raised serum levels of calcium, a reduction of the GFR, and rarely skeletal symptoms. During surgical intervention it is essential that all the parathyroid glands are explored. A histological differentiation between one or several adenomata and diffuse hyperplasia of all the glands is sometimes difficult. In diffuse parathyroid hyperplasia all but one half of a parathyroid gland are removed. Recently, patients have been totally parathyroidectomised and the glandular tissue transplanted into a forearm (35). If too much tissue is transplanted it can be removed relatively easily; on the other hand permanent hypoparathyroidism may result which requires a lifelong substitution with D-vitamins (10).

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