Laboratory Diagnosis of Parathyroid Tumors

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ABSTRACT

The development of hyperparathyroidism (HPT) is presented as well as various problems and possible solutions.

Introduction

More than with many other diseases, the laboratory has played a major role in providing clinicians with a firm base for the diagnosis of hyperparathyroidism (HPT). Automated methods for the assay of serum calcium and phosphorus have facilitated the screening of large segments of the population for hypercalcemia but have also created a problem by uncovering many cases of asymptomatic ("biochemical") HPT. At the other end of the spectrum, there are hyperparathyroid patients with renal stones who have either a very mild hypercalcemia or normocalcemia.

Despite the valuable diagnostic tools contributed by the laboratory, the final decision to operate in the two categories of patients described, i.e., with "biochemical" HPT and those with normocalcemia, has to be based on the integration of data obtained from the history and examination of the patient and from the various analytical, immunological, radiological and histological tests, and therefore still hinges primarily on the experience of the clinician.

When the common symptoms of HPT or significant hypercalcemia are present, the need for exploration is clear. The indications for operative correction in patients with "biochemical" HPT, however, are poorly defined. In some instances, the HPT may indeed undergo a spontaneous remission and never require correction; in other cases, the progress of renal stone disease or nephrocalcinosis may be so insidious as to entail significant degrees of renal damage before its presence is recognized.

The absence of overt symptoms may be misleading. In fact, some of the interesting facets of HPT are the remarkable sense of well-being, the recovery of physical strength, the subtle but significant changes in personality and/or the sense of rejuvenation and alertness that many patients observe after parathyroidectomy. Some symptoms are so gradual in their development that the patients hardly realize they have had them until after their hypercalcemia has been corrected. Here again, the decision to explore will greatly depend upon the experience and the philosophy of the clinician.
Recent Developments

Incidence

A significant increase in the incidence of HPT has recently been noted in North America and Europe. This observation is probably valid, although difficult to substantiate. Among the reasons may be the screening of larger numbers of patients for hypercalcemia with automated methods, the increased awareness that this is not a rare disease, the frequent use of therapeutic agents such as thiazide diuretics, the concentration of large segments of the population in the urban regions, changes in the electrolyte and mineral content of the water supply and undoubtedly other factors as yet unknown.

Immunoassay of Parathyroid Hormone

The increasing perfection and wider availability of parathormone immunoassay based on natural or synthetic human antigen may open new horizons in the diagnosis of HPT. This will eventually require a new set of criteria, for the improved techniques will lead to more frequent findings of high levels of circulating parathormone. This elevation may be due to physiological conditions or to other diseases and need not constitute per se an indication for parathyroidectomy.

Changes in Histopathologic Patterns and Classification

The histopathologic patterning of the glands removed from patients with HPT is also undergoing a change. This has been the source of controversy and confusion in the various attempts at a pathological classification. The single “adenoma,” formerly reported in over 80 percent of the cases, is no longer a prevalent histopathological finding. Current views call for a less rigid classification than the classic “normal-hyperplastic-adenoma-carcinoma.” Today, we realize that combinations of these morphologic states occur in the same patient and occasionally even within the same gland. Adenoma, hyperplasia and, occasionally, even uninvolved glands may exist concurrently. The finding of “multiple gland involvement” has increased in frequency owing to explorations in the earlier disease stages and to more complete histological examination of the glands. The study of hyperplastic parathyroid parenchyma has disclosed transitions between all three of the main cell types. These intermediate forms are not easily categorized.

There seems to be little correlation between the main histologic designation of predominant parathyroid cell types and the intensity or symptomatology of a patient’s disease. It is, therefore, imperative to examine histologically all four parathyroid glands at exploration and, since the definitive pathologic designation is difficult to determine from frozen sections, it is advisable to resect the three largest glands and a portion of the fourth one and to leave in situ a vascularized 50 to 75 mg segment of the latter. This may be the only way to reduce the high recurrence rate of 15 to 100 percent, noted in previous series, where “the adenoma” has been excised.

Many difficulties have been encountered in categorizing and correlating the histopathological picture with the clinical symptomatology in the attempt to differentiate between the various clinical patterns and expressions of HPT. Lloyd differentiates between patients who have primarily stone, bone or “chemical” disease. However, most other observers have been unable to confirm such an attractive simplification and to correlate one variety or the other with involvement of the superior or inferior parathyroid glands and their separate embryologic derivation.

Refinements in Radiologic Techniques

The radiologic findings in patients with long-standing HPT may be almost diag-
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BONE DENSITY VS. AGE FOR NORMAL AND HYPERPARATHYROID MALES

Figure 1. Bone density in hyperparathyroid males. The curve represents the normal range for males, with the standard error of the means. Each dot represents a proven case of hyperparathyroidism. (Courtesy of Dr. Harry K. Genant, Department of Radiology, University of Chicago)

Diagnostic. However, in the vast majority of these patients the roentgenologic bone survey and the serum alkaline phosphatase are normal. A variety of techniques for determining the mineral content of bone and its decrease has been perfected. Bone densitometry can detect minimal degrees of osteoporosis and provide an overall index of calcium balance (figures 1 and 2). Progressively falling values of bone density over a period of several months, an indication of negative calcium balance, may therefore furnish strong additional evidence in patients already suspect of HPT.

Fine-grained industrial films and minute radiologic examination of the bones of the hands permit the detection of very early changes, such as minimal degrees of subperiosteal resorption and "tunnelling," which are consistent with HPT, but cannot be detected by conventional techniques (figures 3 and 4).

INVASIVE TECHNIQUES FOR LOCALIZATION OF PARATHYRIDS

Preoperative radiologic localization is of no special value to the experienced surgeon since it only spots large tumors, which are usually found anyway at exploration. It is the small ones that are more likely to be overlooked. The methods commonly used are: (1) angiographic localization by bilateral injection of radio-opaque dye into the thyrocervical artery, (2) isotopic localization by bilateral injection of high concentrations of Se\textsuperscript{75} selenomethionine into

Figure 2. Bone density measurements before and after operative correction of the hyperparathyroidism. (Courtesy of Dr. Harry K. Genant, Department of Radiology, University of Chicago)
the thyrocervical artery and (3) determination of parathormone levels in venous samples obtained at specific sites from the internal jugular and innominate veins and their inferior thyroid branches bilaterally through catheterization.

It should be emphasized that these methods are invasive and carry a significant risk to the patient. They should be limited to such situations, for instance, where the disease is still suspected after an unproductive exploration.

Non-Invasive Techniques for Localization of Parathyroids

Sizeable tumors can, on occasion, be localized by such conventional techniques as barium swallow (figures 5 and 6), laminography of the superior mediastinum, $^{131}$I thyroid scan (figure 7) and the intravenous injection of $^{75}$selenomethionine.

The most useful of these is the barium swallow, which will delineate even subtle degrees of compression of the upper esophagus by tumors in the superior posterior mediastinum.

**Special Problems**

Coexisting, but ostensibly unrelated endocrinopathies and malignancies that elaborate parathormone and vitamin-D like sterols may complicate the diagnosis of HPT. Special problems include (1) hyper-
calcemia, (2) compensatory hyperparathyroidism, (3) parathyroid carcinoma, (4) hyperthyroidism co-existent with hyperparathyroidism, (5) acute pancreatitis, (6) hypertension and thiazide intake and (7) surgery.

HYPERCALCEMIA

The principal causes of hypercalcemia are: hyperparathyroidism; other neoplastic diseases; hyperthyroidism; hypothyroidism; Cushing's syndrome; milk-alkali syndrome; vitamin D intoxication; sarcoidosis and Paget's disease. Occult malignancies pose the greatest diagnostic challenge. The hypercalcemia of these tumors is secondary to the over-production of a parathormone-like substance that is immunologically similar, if not identical, to parathyroid hormone. The fact that the parathyroid glands in such patients are frequently hyperplastic, even in the presence of hypercalcemia, is intriguing and suggests that these tumors may also secrete a substance that stimulates the parathyroid glands. Parathyroid tumors, causing severe hypercalcemia, have been excised from patients with long-standing metastatic breast cancer, with complete remission of the hypercalcemia and its associated symptoms.8

Mammary cancer accounts for approximately 50 percent of hypercalcemia associated with malignant tumors.18 In most instances this hypercalcemia is thought to be caused by the secretion of vitamin D-like sterols, rather than parathormone.7

Hypercalcemia is found in over 20 percent of patients with hyperthyroidism if
ionized calcium is determined or the total calcium values are corrected for the accompanying low serum albumin. The determination of serum parathormone should be instrumental in differentiating the hypercalcemia of this disease from that of HPT.

Minimal hypercalcemia may exist in hypothyroidism. It is more likely to occur during the transition to an euthyroid state after treatment with small doses of thyroid hormone has been started.

In Cushing's syndrome, the hypercalcemia may be secondary to increased calcium resorption from bones which is produced by the high circulating levels of cortisone or by a parathormone-like substance secreted by the hyperplastic or adenomatous adrenals. Once the syndrome is corrected by adrenalectomy, serum calcium reverts to normal.

In the milk-alkali syndrome and in vitamin D intoxication, the history is the key to the diagnosis. Hypophosphatemia is usually absent.

The hypercalcemia of sarcoidosis is believed by some to be the result of increased sensitivity to vitamin D and may represent a form of vitamin D intoxication. It is most frequent in warmer climates, since exposure to sunlight will enhance the endogenous synthesis of vitamin D. However, hyperplasia and adenoma of the parathyroid glands occur with greater frequency in sarcoid patients than can be attributed to chance alone.\textsuperscript{3,4} Parathyroidectomy in patients with co-existent sarcoidosis and HPT corrects the hypercalcemia. The hypercalcemia of sarcoidosis alone is not accompanied by hypophosphatemia and usually responds to the administration of 40 to 60 mg of prednisone a day for five or six days.

In Paget's disease, hypercalcemia is generally noted when a patient with extensive and widespread bone disease is immobilized or in cases complicated by osteogenic sarcoma. HPT seems to accompany Paget's disease in about 3 percent of the cases, which is more frequent than can be explained by chance alone\textsuperscript{11} (as was the case with sarcoidosis). However, most of these patients had the disease only to a minimal degree and their hypercalcemia may have been due to the coexisting HPT and was corrected by parathyroidectomy.

**COMPENSATORY HYPERPARATHYROIDISM**

The differentiation of primary from compensatory HPT has been the subject of many discussions. While the distinctions may be artificial and contrived, they are nevertheless helpful in arriving at a diagnosis. Thus, there still appears to be some merit in weighing several differential diagnostic features of the classic “primary hyperparathyroid” patient and the chronic nephritic with recognized compensatory hyperplasia. When the latter is associated with parathyroid hyperplasia, the serum calcium does not generally exceed normal levels, and metastatic calcifications in soft tissues other than the kidneys are far more common. This may reflect easier precipitation of calcium phosphate crystals owing to
the hyperphosphatemia of chronic renal failure. This phenomenon has never been seen in primary HPT with intact renal function. On the other hand, pseudo-gout and chondro-calcinosis may occur with primary HPT but not with compensatory HPT. Many investigators believe that if calcium infusion can suppress elevated parathyroid hormone levels to normal, an autonomous "adenoma" is not present. It is less certain whether or not parathyroid hormone suppression per se can distinguish purely compensatory HPT from eucalcemic primary HPT secondary to diffuse hyperplasia of all four glands.

Finally, it has been suggested that raising the serum calcium into the hypercalcemic range by the use of pharmacologic doses of vitamin D and calcium for several weeks will increase the tubular reabsorption of phosphorus in secondary HPT, but only if the renal failure is not due to primary HPT. The authors consider this test, however, far too hazardous to perform in patients with already compromised renal function and thus cannot endorse it.

**Parathyroid Carcinoma**

The incidence of parathyroid carcinoma found at operation is less than 2 percent in most series. In ours, it occurred twice in 120 explorations. Some of these carcinomas may not secrete any parathormone. Functioning parathyroid carcinomas may present diverse clinical courses, ranging from rapid exacerbation with death in a few months caused by sequelae of the severe hypercalcemia, to a slowly progressing disease with local recurrence and mild hypercalcemia (figure 6).

**Hyperthyroidism Co-Existential with Hyperparathyroidism**

The diagnosis of HPT is especially difficult in the presence of hyperthyroidism since hypercalcemia and hypercalciuria occur in both diseases. The patient must be in euthyroid state before HPT can be established. It is best to treat the patient with radioactive iodine, to allow the thyroid gland to atrophy and then to proceed with the confirmatory tests and exploration. Preparation or treatment with antithyroid drugs is not indicated in such situations for two reasons. First, these drugs increase the already high vascularity of the enlarged thyroid gland (although this effect can be partially offset with Lugol's solution and thyroxine). A parathyroid exploration would then be ill-advised. Secondly, since these agents stimulate the parathyroid glands, they impede the diagnosis of primary HPT.

**Acute Pancreatitis**

In the course of acute pancreatitis, many patients will display hypophosphatemia and hypocalcemia. During recovery, there may be a rebound hypercalcemia. In this phase, hypercalcemia and hypophosphatemia may coexist for several days to a few weeks. This is usually not due to primary HPT but to an increase in parathyroid hormone secretion, secondary to the pre-existing hypocalcemia, and probably also to an increase in circulating glucagon.

**Hypertension and Thiazide Intake**

A significant number of patients with HPT have coexisting essential hypertension. When hypercalcemia and hypophosphatemia are detected in patients treated with thiazide diuretics, these drugs should be discontinued for at least two weeks before the diagnostic studies are begun, since they can produce hypercalcemia and hypophosphatemia in patients as they do in experimental animals.

**Diagnosis of Hyperparathyroidism at Surgery**

There is no substitute for the experienced surgeon who has a clinical and research in-
terest in parathyroid disease and who has participated in the evaluation to the patient and in the decision to perform exploratory surgery. The identification of at least four glands is of utmost importance. Supernumerary glands, normal or enlarged, are found occasionally. All parathyroid tissue should be examined by frozen-section microscopy, mainly to identify it. Before the conclusion of the exploration, the surgeon must decide whether or not the amount (weight and size) of the parathyroid tissue that has been removed is compatible with the diagnosis and the degree of hypercalcemia, since there is a direct correlation between the calcium level and the size of the glands. In assessing the amount of excised tissue, the percentage of fat cells seen on frozen section must be taken into account. If this amount is not in keeping with the expected results, the patient should be considered a pathological rather than a physiological phenomenon and requires remedial action.

**Resumé and Conclusion**

Total and ionized serum calcium determinations are still the most important and useful tools in the armamentarium of the clinician in the diagnosis of most cases of HPT. In all probability this will remain so in the foreseeable future for the very simple reason that circulating calcium is a measure of the effects of several hormones and many other factors. A rise in the circulating level of a given hormone *per se* does not constitute an indication for correction. However, a persistent rise in serum calcium should be considered a pathological rather than a physiological phenomenon and requires remedial action.

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