Recurrent hyperparathyroidism: a study of 3 cases with evaluation of some pathogenetic and clinical aspects

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Summary: Three patients with recurrent hyperparathyroidism (15, 8 and 3 years respectively, after the first operation) are described in order to establish the causes and define the clinical characteristics of the disease.

The observation that in the present series recurrent hyperparathyroidism was associated either with an adenoma (two cases) or a carcinoma (one case), appears to stress the possibility of the pathological involvement of one gland even though recurrent hyperparathyroidism should be considered due to the chronic extrinsic stimulation of the parathyroid glands. The severity of the clinical and metabolic picture observed at the time of the first diagnosis and/or at the time of recurrence together with the simultaneous presence of bone and stone disease in the patients described is of particular interest.

The cases reported underline the importance of carrying out careful metabolic investigations in patients with hyperparathyroidism not only before but also for a prolonged period of time after operation.

Introduction

The term recurrent hyperparathyroidism is generally used to define the reappearance of clinical and metabolic evidence of the disease six1 or twelve2 months after the initial operation.

Recurrent hyperparathyroidism has been described both in the genetic (familial) and sporadic (non-familial) forms of the disease and may be considered a rare occurrence appearing in between 0% and 3%3,4,5 of patients submitted to surgery. In our series of 102 patients with primary hyperparathyroidism confirmed at surgery, recurrence of the disease was observed in 3 cases.

Data from these patients have been analysed in an attempt to establish the causes and define the clinical picture of the recurrence.

Case reports

Case 1

A 38 year old male, having originally presented at the age of 17 with a mandibular giant cell tumour, had been submitted to the removal of a lower right parathyroid adenoma when 23 years old. A biopsy of the lower left parathyroid showed no abnormalities on histological examination. At follow-up the main parameters of calcium-phosphorus metabolism (notably serum and urinary calcium; serum immunoreactive parathyroid hormone, assayed on two occasions) evaluated at regular intervals after surgery for a period of 15 years, were always within normal limits.

The patient developed arterial hypertension in 1977; X-ray examination on this occasion revealed the presence of a radio-opaque stone in the left renal pelvis. In January 1985, following a sharp pain in the left ankle with functional impairment, laboratory tests were carried out which demonstrated hypercalcaemia and hypophosphataemia (Table I). The patient was, therefore, hospitalized in our Institute and submitted to surgical exploration of the neck. The left upper parathyroid, 0.8 cm in diameter, was removed. The parathyroid contained a haemorrhagic cyst. Histological examination revealed that it was mostly composed of transitional oxyphil cells forming cords and acini. A rim of normal parathyroid tissue was recognizable on one side of the specimen. A diagnosis of parathyroid adenoma was made. Following surgery, serum calcium concentrations fell to 1.81 mmol/l by the sixth post operative day; the patient is now receiving 50 μg of 1.25 dihydroxyvitamin D₃.

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**Case 2**

A man born in 1935 had been hospitalized for right renal colic at 31 years of age. A diagnosis was made of primary hyperparathyroidism (Table I); a year later, surgical exploration of the neck was carried out and a hard mass, the size of an almond with the vascular peduncle completely outside the thyroid capsule, was excised from the lower left parathyroid site. Histological diagnosis was of adenoma even though the cells were in a trabecular pattern and the stroma consisted of dense bands of fibrous tissue. There was no evidence of mitoses, local invasion or metastases. Unfortunately, review of the original material was not possible. Eighty years after the first operation (normocalcaemia was documented on three occasions during this period) the patient suffered from left renal colic. On this occasion systemic arterial hypertension was also observed. On the basis of biochemical investigations primary hyperparathyroidism (Table I) was again diagnosed. Surgical exploration of the neck revealed the presence, at the level of the lower pole of the left thyroid lobe, of a firm, greyish mass, 3.0 by 2.0 by 1.0 cm in diameter, with irregular borders and surface, adhering to the area below. The lymph nodes did not appear enlarged and were not removed. On histological examination the tumour was composed of uniform large epithelial cells arranged in a trabecular pattern, and some mitoses were observed. A dense fibrous stroma was present and the striated muscle adherent to the parathyroid was infiltrated. The tumour was in exactly the same place as before and fragments of suture surrounded by foreign body giant cells were present on one of its sides. The diagnosis was of parathyroid carcinoma in spite of the absence of metastases.

Following surgery, serum calcium values dropped to below 1.25 mmol/l. In July 1981, after at least two years of normal serum calcium, the patient consulted a doctor complaining of fatigue and muscle weakness. Blood pressure of 210/160 mmHg was revealed on physical examination and a diagnosis of hyperparathyroidism was made on the basis of laboratory analyses (Table I). Surgical exploration of the neck was unsuccessful as was treatment with human calcitonin. The patient died 6 months later following a sudden episode of left ventricular failure. Unfortunately, autopsy studies were not carried out.

**Case 3**

A female patient, born in 1954, complained of bone and joint pains at the age of 15 years. One year later, following renal colic, a stone was revealed in the right kidney; a few months later a pathologial fracture of the left radius occurred. At 17 years of age, the patient was hospitalized following a further episode of right renal colic and found to have hyperparathyroidism (Table I). Values reported refer to measurements carried out simultaneously. Variations in the normal values for both serum immunoreactive parathyroid hormone and alkaline phosphatase activity depend upon the different assay techniques used during the observation period.

<table>
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<tr>
<th>Age</th>
<th>Sex</th>
<th>Serum pHPTH (nmoll/l)</th>
<th>Serum Ca (mmoll/l)</th>
<th>Serum Cr (mmoll/l)</th>
<th>Serum P (mmoll/l)</th>
<th>24-h Urinary P (mg/24-h)</th>
<th>24-h Urinary Ca (mg/24-h)</th>
<th>TmPO4/GFR (mmoll/l)</th>
<th>TmCa/GFR (mmoll/l)</th>
<th>OHPr (mmoll/l)</th>
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</table>

**Table 1**: Values of the main parameters of calcium-phosphorus metabolism in patients submitted to surgery for recurrent hyperparathyroidism. Values reported refer to measurements carried out simultaneously. Variations in the normal values for both serum immunoreactive parathyroid hormone and alkaline phosphatase activity depend upon the different assay techniques used during the observation period.

**Abbreviations** refer to:
- Ca: calcium; P: phosphate; pHPTH: immunoreactive parathyroid hormone; A.P.: alkaline phosphatase activity; Fr: creatinine; OHPr: OHP ratio.
- The normal range for serum pHPTH is 4.0-6.0 mmol/l.
- The normal range for serum Ca is 2.5-3.0 mmol/l.
- The normal range for serum Cr is 0.8-1.2 mmol/l.
- The normal range for serum P is 0.8-1.4 mmol/l.
- The normal range for 24-h Urinary P is 0.3-0.8 mmol/l.
- The normal range for 24-h Urinary Ca is 0.1-0.3 mmol/l.
- The normal range for TmPO4/GFR is 1.0-2.0 mmol/l.
- The normal range for TmCa/GFR is 1.0-2.0 mmol/l.
- The normal range for OHPr is 0.4-0.8 mmol/l.
- The normal range for serum pH is 7.35-7.45.
- The normal range for serum Ca is 2.5-3.0 mmol/l.
renal colic and a diagnosis was made of primary hyperparathyroidism. On exploration of the neck an orange-brown mass weighing 18.7 g and measuring 4.1 by 3.3 by 2.0 cm was removed from the lower left area. Histological examination revealed parathyroid adenoma, formed mostly by transitional oxyphil cells. Biopsy of the left upper parathyroid revealed no histological abnormalities.

Following parathyroidectomy serum calcium values returned to normal levels. In March 1976, after about 3 years of documented normocalcaemia, the patient was again hospitalized due to the onset of dyspepsia, heartburn, nausea, vomiting and constipation. Upon clinical examination, a mass the size of an olive was palpable adhering to the right thyroid lobe. The results of the laboratory tests are shown in Table I. At surgery the lower part of the right lobe of the thyroid was removed together with a pliable, orange-brown mass measuring 2.0 by 1.5 by 1.0 cm. A histological diagnosis of chief cell adenoma of the lower right parathyroid was made. Ten years after the last operation the patient is still enjoying excellent health.

Discussion

From an analysis of the clinical cases presented it is possible to draw some conclusions regarding the pathogenetic aspects and the clinical characteristics of recurrent hyperparathyroidism.

The patients in this report presented with a recurrence of the disease respectively 15, 8 and 3 years after the first operation. During this interval serum calcium levels were always within normal limits; furthermore, in all the patients studied, there were no recognizable stimuli known to induce hyperplasia of the parathyroid glands, thus satisfying the criteria for true recurrence of the disease. In this respect, it is interesting to note that a recent report has demonstrated parathyroid mitogenic activity in plasma from patients with familial multiple endocrine neoplasia type 1. This hypothetical humoral factor, possibly responsible for parathyroid gland hyperfunction in this disorder, may also be responsible for the recurrence of the disease in some patients with primary hyperparathyroidism.

However, the observation that in the present series recurrence was associated with an adenoma in 2 cases and with carcinoma of the parathyroid glands in one case, appears to stress the possibility of the pathological involvement of only one gland, even though recurrent hyperparathyroidism should be considered to be due to chronic extrinsic stimulation of the parathyroid glands.

As far as Case 1 is concerned, the histological diagnosis of parathyroid carcinoma at the second operation is supported by the criteria now considered necessary for diagnosis. In addition, this case raises the problem of parathyroid carcinoma diagnosis when local invasion or metastases are missing. Unfortunately, the impossibility of revising the original material does not allow a definitive assessment of the first tumour. The reported pathological features suggest, however, that it was carcinoma although local invasion of mitoses were not present. The same localization of both tumours, as demonstrated by the finding of suture, could be ascribed to spillage of parathyroid tissue during surgery even if the tumour had been an adenoma. However, local malignant recurrence in parathyroid carcinoma is more frequent than metastases.

It is worth emphasizing the severity of the clinical and metabolic picture observed at the time of the first diagnosis and/or at the time of recurrence in the three patients described; this severity was documented by the high serum calcium levels and the marked skeletal involvement revealed both by radiological and biochemical studies. From the data available, it is difficult to ascertain whether this represents a characteristic feature of recurrence; it is necessary to bear in mind that in the past it was easier to detect more severe disease. At present the occasional finding of hypercalcaemia appears to represent the main reason for the patient seeking medical advice.

The simultaneous presence of bone and stone disease observed in the patients described is particularly interesting: indeed at present the involvement of both parathyroid hormone target organs is as rare an observation as it was in the past.

Finally, the cases described underline the importance of carrying out careful metabolic tests in patients with hyperparathyroidism not only before surgery, but also for a prolonged period after the operation.

Acknowledgements

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