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Primary hyperparathyroidism with normal serum intact parathyroid hormone levels

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Summary

To evaluate the features of primary hyperparathyroidism (HPT) with normal serum intact parathyroid hormone (iPTH) levels, we studied 271 consecutive patients undergoing surgery for primary HPT. In 20 patients, serum iPTH levels were within the normal range (10–65 ng/l). In their records, the most common clinical features were fatigue ($n=13$), polyuria ($n=6$), renal stone ($n=5$), and hypertension ($n=5$). Mean serum calcium and phosphorus were 2.78 and 0.85 mmol/l, respectively: 14 had serum phosphorus within the normal range. Mean serum iPTH was 48.5 ng/l, and was <45 ng/l in nine patients. Cervical ultrasound demonstrated a parathyroid adenoma in nine, and was normal in four. Tc sestamibi parathyroid scintigraphy always demonstrated an adenoma (9/9). In eight patients, normal iPTH values delayed diagnosis. Physicians should be aware of the possibility of HPT in patients with hypercalcaemia, even when serum phosphorus and iPTH levels are within the normal limits. Particularly, HPT cannot be excluded when serum iPTH levels are below the upper part of the normal range. In such cases, cervical imaging, which has the same sensitivity as in other HPT, should be undertaken. These explorations are useful, because many patients are symptomatic and can take advantage of surgery.

Introduction

Primary hyperparathyroidism (HPT) is frequently recognized following the incidental discovery of hypercalcaemia. In the past years, diagnosis has been facilitated by the development of radioimmunoassays measuring intact parathyroid hormone (iPTH). However, in some cases, iPTH levels are within the normal values, possibly leading to diagnosis difficulties. Numerous authors have already reported that iPTH can be in the normal range in cases of primary HPT. However, very few data are available regarding the frequency and the clinical, laboratory, imaging, and pathological characteristics of primary HPT with normal iPTH levels. The aim of this work was to evaluate such primary HPT.

Methods

We evaluated 271 consecutive cases of surgically proved primary HPT treated at the University Hospital of Dijon, Burgundy, France, from 1991 to 1998. All neck explorations were performed through a transverse cervical incision. All four parathyroid glands were explored and identified. Adenomas were excised. Diffuse parathyroid hyperplasia were treated by subtotal parathyroidectomy. The records of the patients with normal serum iPTH values (radioimmunoassay, Nichols Institute, normal range 10–65 ng/l) were selected and analysed retrospectively. Patients were selected only if all determinations of iPTH were within the normal values.

Twenty patients (7.4%) had serum iPTH within the normal values. There were 14 women (mean age 62 years $\pm$19.6 SD) and six men (mean age 47.2 years $\pm$17.9 SD).

Twenty-seven patients had one normal serum iPTH value, with other values above normal, and were not included. The iPTH with normal values represented a continuum of a normal distribution (mean iPTH for the 271 cases = 153.8 ng/l $\pm$156).

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The following data were recorded: age, gender, clinical features, serum calcium, phosphorus, creatinine, iPTH, 24-h urinary calcium and phosphorus. The results of cervical ultrasound and of 99mTc sestamibi parathyroid scintigraphy were noted. The time-interval between discovery of hypercalcaemia and diagnosis of HPT was computed. Pathological results were reviewed.

Results

Nineteen patients (95%) had pre-operative symptoms. The most common symptoms were neuropsychiatric disturbances, including fatigue (13 patients), nervous breakdown (3 patients) and confusion (2 patients). Other symptoms and signs included polyuria (6 patients), renal stones (5 patients), hypertension (5 patients), bone pain (2 patients), calcium pyrophosphate dihydrate microcrystalline arthritis (1 patient), peptic ulcer (1 patient), and weight loss (1 patient). No patient had multiple endocrine neoplasia.

Laboratory tests

Pre-operative serum calcium was raised in 19/20 patients (mean 2.78 mmol/l $\pm$0.3 SD; range 2.5–3.2, normal range 2.3–2.6). In the patient with normal calcium and iPTH levels, the diagnosis was suspected on clinical presentation, with serum calcium and iPTH levels in the upper part of the normal range, and was made after cervical imaging. In contrast, serum phosphorus was low in only 6/20 patients (mean 0.85 mmol/l $\pm$0.24 SD). Urinary calcium was determined in all patients. Hypocalciuria was never observed. Unfortunately, since patients were referred from all around Burgundy, the determination of urinary calcium was, in some instances, not performed in our centre. Thus, in some patients, the results of urinary calcium (and phosphorus) were recorded as normal-increased-decreased, but we do not know the exact values. Consequently, 24-h urine calcium and phosphorus could not be correctly evaluated.

Serum creatinine was normal in 11/11 patients (no data for the remaining nine patients).

Due to patient selection, serum iPTH levels were within the normal range in all cases. Mean serum iPTH was 48.5 ng/l $\pm$10.2 SD (range 28–61). In most cases (11 patients, 55%), serum iPTH levels were 45–65 ng/l, although lower levels (30–45 ng/l) were not uncommon (8 patients, 40%). For one patient, serum iPTH level was $<$30 ng/l (28 ng/l). This patient presented with serum calcium of 2.97 mmol/l and serum phosphorus of 0.8 mmol/l. Surgery removed a 580 mg adenoma.

Cervical imaging

Seventeen patients underwent pre-operative cervical imaging, including cervical ultrasound (13 patients) and 99mTc sestamibi parathyroid scintigraphy (9 patients).

Cervical ultrasound demonstrated a parathyroid adenoma in nine (69.2%), and failed to show any abnormality in four (30.8%). For all patients with abnormal ultrasound, the observed adenoma was confirmed by surgical exploration. However, in two of these patients, surgery demonstrated multiple adenomas that were not showed by ultrasound. For the four patients in whom cervical ultrasound was normal, surgery showed a single adenoma (two patients), a double adenoma (one patient), and a parathyroid diffuse hyperplasia (one patient).

^{99m}Tc sestamibi parathyroid scintigraphy was performed nine times, and always demonstrated an adenoma. There was a good correlation between parathyroid scintigraphy and surgical exploration, except for one patient, in whom surgery demonstrated the suspected adenoma, but also found another adenoma not previously identified.

Histopathology

HPT was due to a single adenoma in 13 patients (65%), to multiple adenomas in three patients (15%), and to diffuse parathyroid hyperplasia in four patients (20%). The mean$\pm$SD mass of adenomas was 587$\pm$850 mg.

Diagnosis

The diagnosis of HPT was made by a general practitioner (four patients), a rheumatologist (four patients), an endocrinologist (seven patients), or others (five patients), and confirmed by surgery. No recurrence was observed during post-surgery follow-up.

The time-interval between discovery of hypercalcaemia and diagnosis of HPT was $<$1 month for nine patients, from 1 month to 1 year for four patients, and $>$1 year for seven patients (mean 17.8 months $\pm$32.7 SD). For eight patients, the diagnosis of HPT was initially missed on the basis of normal serum iPTH.

Discussion

Our results show that, in patients with HPT, serum iPTH levels within the normal range are not unusual. Our proportion of patients with normal serum iPTH level was 7.4%, similar to results elsewhere.[1] Moreover, our patients were seen in a surgery department, inducing a recruitment bias. Since

patients with asymptomatic mild HPT rarely undergo surgery, our series may well underestimate the frequency of HPT with normal serum iPTH levels.

HPT with normal serum iPTH levels appears to have no peculiar clinical presentation. Our results were in accordance with those of large series of patients with HPT.[2–7] The small percentage of asymptomatic patients might be due to surgical recruitment. However, primary asymptomatic HPT is less frequent than is usually believed.[2] Our data show that primary HPT with normal serum iPTH levels is not always mild, can be symptomatic, and can need surgical treatment.

Serum calcium was usually increased. However, this increase was often moderate (mean 2.78 mmol/l). Such a finding is not surprising, since there is a positive relationship between serum calcium and serum iPTH levels in primary HPT.[3,8] However, serum iPTH was normal in some patients with higher levels of serum calcium (up to 3.2 mmol/l in our series), indicating that in patients with significant hypercalcaemia, normal serum iPTH levels do not eliminate HPT. Serum phosphorus was often normal (70%), possibly making the diagnosis more difficult. Due to selection of patients, serum iPTH levels were always within the normal range. As expected, most serum iPTH levels were in the upper part of the normal range (55% >45 ng/l). In patients with hypercalcaemia, serum iPTH levels in the upper part of the normal range should be considered as inappropriate and should lead the physician to suspect HPT. However, our results show that serum iPTH levels are not always in the upper part of the normal range. Consequently, the diagnosis of HPT can not be eliminated when serum iPTH levels are in the middle part of the normal range (or in the upper part of the inferior third, such as was observed in one of our patients).

Histopathology was in accordance with the literature.[2,4,7] The frequency of parathyroid hyperplasia was high (20%), but not enough to conclude that the proportion of hyperplasia is higher in primary HPT with normal serum iPTH levels than in other HPT. The weight of adenomas might be lower in primary HPT with normal serum iPTH levels than in other HPT. The mean weight (587 mg) was low in comparison with other series.[9] Such a finding is not surprising, since there is a positive relationship between serum iPTH levels and parathyroid glandular weight and size in primary HPT.[3,4] Surprisingly, despite the low mean weight, the sensitivities of cervical ultrasound and ^{99m}Tc sestamibi parathyroid scintigraphy were comparable to those observed in the entire HPT group.[10,11]

The normal serum iPTH values delayed diagnosis in a significant proportion of patients (40%), although a number of authors have already reported that iPTH is sometimes normal in primary HPT. The frequency of moderate increases in serum calcium and normal serum phosphorus probably adds to the diagnostic difficulties.

In conclusion, physicians should be aware of the possibility of HPT in patients with hypercalcaemia, even when serum phosphorus and iPTH levels are within the normal limits. Particularly, serum iPTH levels in the upper part of the normal range should be considered as inappropriate and should lead to the suspicion of HPT. Moreover, the diagnosis of HPT cannot be eliminated when serum iPTH levels are in the middle part of the normal range (or in the upper part of the lowest third). In such cases, after evaluation of urinary calcium, to eliminate familial hypocalciuric hypercalcaemia, other explorations should be undertaken, such as functional tests, and/or cervical imaging, which might have the same sensitivity as in other cases of HPT. Such explorations are useful, because many patients are symptomatic and can take advantage of surgery.

References

1. Ljunghall S, Larsson K, Lindh E, Lindqvist U, Rastad J, Akerström G, Wide L. Disturbance of basal and stimulated serum levels of intact parathyroid hormone in primary hyperparathyroidism. *Surgery* 1991; **110**:47.
2. Udén P, Chan A, Duh QY, Siperstein A, Clark OH. Primary hyperparathyroidism in younger and older patients: symptoms and outcome of surgery. *World J Surg* 1992; **16**:791.
3. Ljunghall S, Hellman P, Rastad J, Akerström G. Primary hyperparathyroidism: epidemiology, diagnosis and clinical picture. *World J Surg* 1991; **15**:681.
4. Nikkilä MT, Saaristo JJ, Koivula TA. Clinical and biochemical features in primary hyperparathyroidism. *Surgery* 1989; **105**:148.
5. Wallfelt C, Ljunghall S, Bergström R, Rastad J, Akerström G. Clinical characteristics and surgical treatment of sporadic primary hyperparathyroidism with emphasis on chief cell hyperplasia. *Surgery* 1990; **107**:13.
6. Heath III H, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. *N Engl J Med* 1980; **302**:189.
7. Chigot JP, Lizana C, Chiche B, Dura C, Menegaux F. Hyperparathyroïdie primaire. Analyse rétrospective de 645 observations. *Sem Hop Paris* 1990; **66**:726.
8. Flentje D, Schmidt-Gayk H, Fischer S, Stern J, Blind E, Buhr H, Herfarth C. Intact parathyroid hormone in primary hyperparathyroidism. *Br J Surg* 1990; **77**:168.
9. Mellière D, Berrahal D, Perlemuter L, Hindie E, Simon D. Hyperparathyroïdies primaires. Relation des symptômes avec l'âge, le sexe, la calcémie, les lésions anatomiques et le poids des glandes. *Presse Med* 1995; **24**:1889.
10. Chou FF, Wang PW, Sheen-Chen SM. Preoperative localization of parathyroid glands in primary hyperparathyroidism. *Eur J Surg* 1997; **163**:889.
11. Pattou F, Huglo D, Proye C. Radionuclide scanning in parathyroid diseases. *Br J Surg* 1998; **85**:1605.